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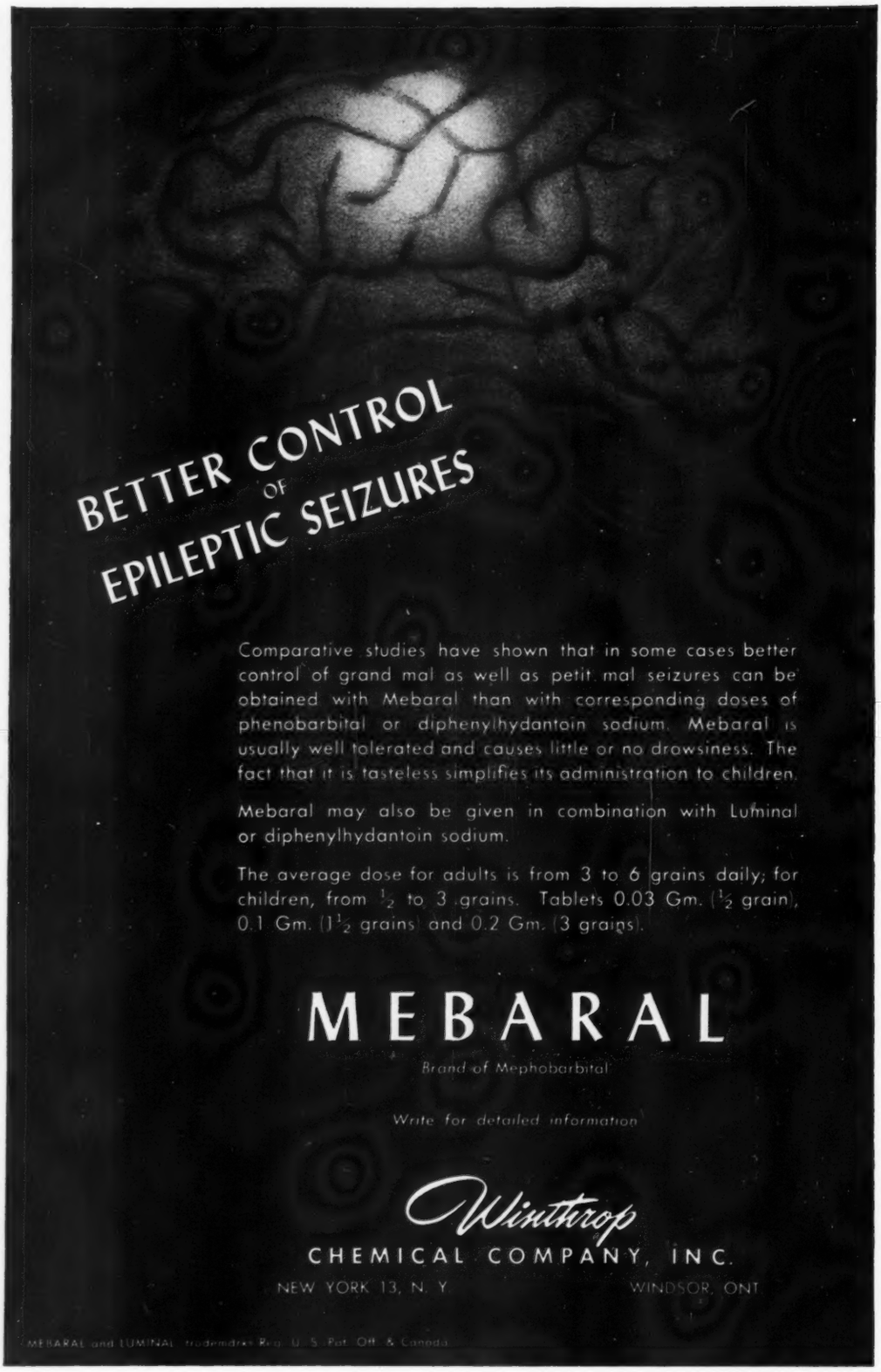
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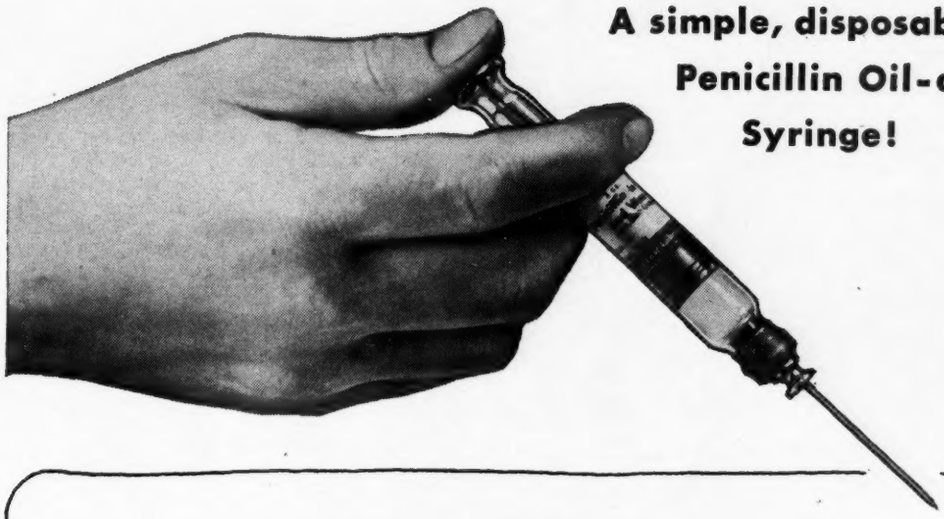

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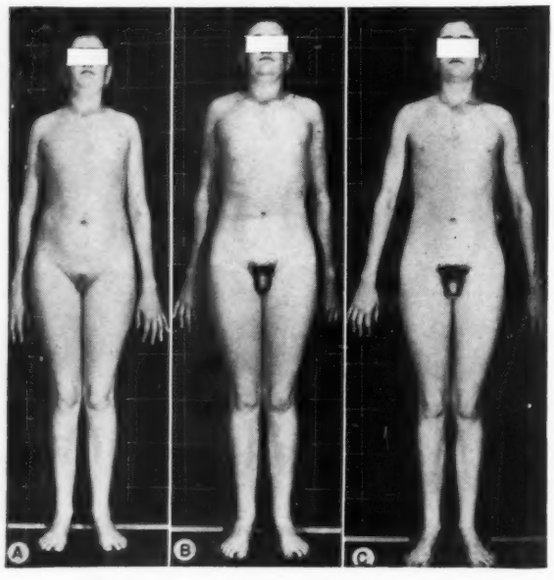

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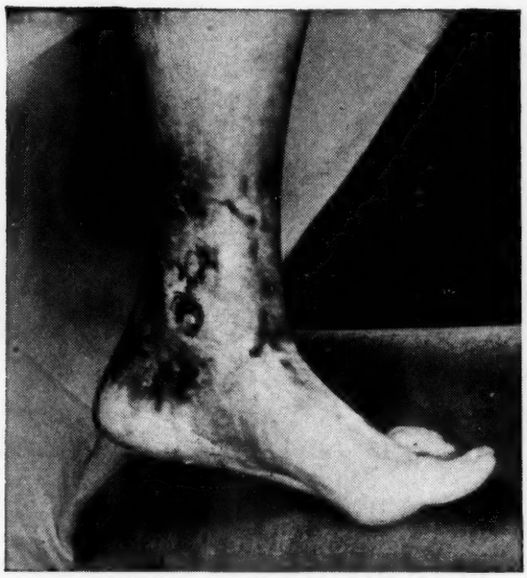

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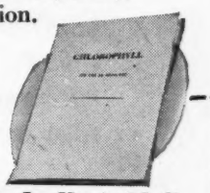

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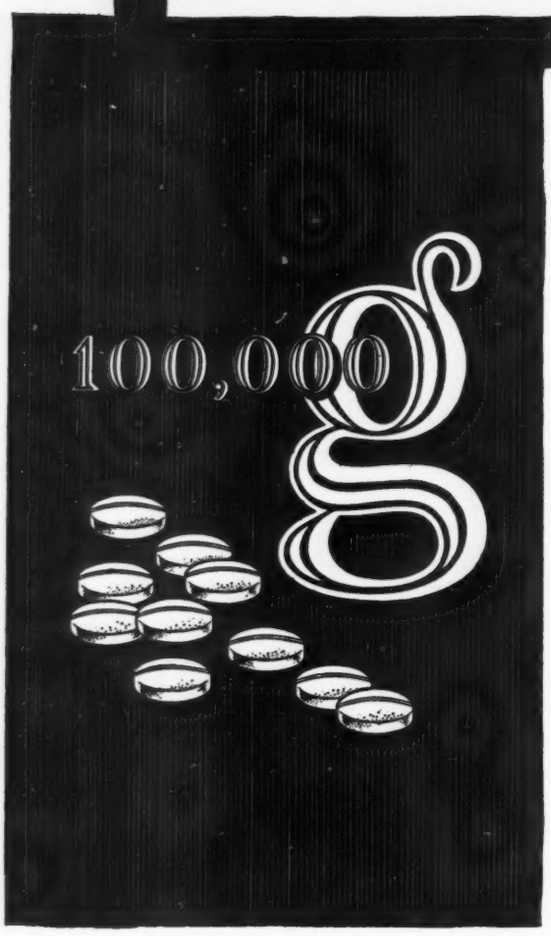

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Editorial

The Thymus and Myasthenia Gravis

SIR Astley Cooper was the real forerunner of a host of investigators who have endeavored without success to demonstrate some active principle or hormone in the thymus. The classical methods of endocrine research designed to produce deficiency symptoms upon removal and evidences of positive effect on administration or surgical transplant have been without results capable of repetition. The outstanding fact about this gland which stimulates interest is that it can be removed from the human subject in its entirety without endangering normal function in any demonstrable manner. There is much clinical evidence to suggest that the thymus has some as yet unknown endocrine function. The gland hypertrophies in the presence of hyperthyroidism, adrenal cortical hypofunction and gonadal hypofunction both in the male and female.

Abnormalities in the thymus are seen with great frequency in myasthenia gravis. Many endocrinological processes have a very definite influence on the course of this disease. The development of pregnancy often leads to a remission of symptoms while many women with myasthenia gravis become worse just before the onset of their menstrual flow. The relationship between myasthenia gravis and disease of the thyroid gland is well known but little understood.

Extirpation of all thymic tissue in patients with myasthenia gravis seemed to be justified for trial as a therapeutic procedure and study of these patients after operation offered hope of obtaining clues as to the function of this gland which has for so long been an enigma. In about 15 per cent of the subjects the therapeutic results have been dramatic and by the use of modern physiological technics concrete evidence has been obtained of a reversion of neuromuscular function to normal. Further study of the clinical course of these patients and physiological studies with normal thymic tissue and with the material removed at operation are promising means for further elucidation of this intriguing problem.

Over 200 patients have now been treated by thymectomy. Many observers have been discouraged by the relative paucity of dramatic results; however, search for further clues as to why some patients are benefited and others are not should lead us not only to a better understanding of the disease but also of the normal processes of neuromuscular function and the various factors influencing it. In summarizing the results thus far from thymectomy, it may be said that those patients operated upon at an early stage of the disease are most likely to improve and that in general strength returns in the trunk and limb muscles more promptly and completely than in those muscles innervated by the cranial nerves. The remission after thymectomy does not depend on the presence of a discrete

tumor of the thymus for one of the most striking cures with complete freedom of symptoms for six years after operation was obtained in a patient with a moderately large, hyperplastic gland.

However, closer study of those patients with a thymoma is indicated. All of the tumors studied in Baltimore have shown varying amounts of neoplastic tissue derived from the epithelial cells of the thymic reticulum in addition to lymphocytic hyperplasia. Very frequently these tumors are not demonstrated by careful radiological examination although they may have reached a rather large size. The rapid increase in the severity of the myasthenia which often occurs in the presence of a thymic tumor is one of the striking observations, suggesting that this gland produces a substance which under certain circumstances interferes with normal function at the neuromuscular junction.

One of the characteristic features of the clinical course of patients with myasthenia gravis before the introduction of neostigmine therapy was the frequency of spontaneous complete remissions. The belief of some observers is that since the introduction of this therapeutic agent the incidence of these spontaneous remissions has diminished. There are still many cases in which the severity of the symptoms fluctuates but complete remissions lasting for any length of time are most unusual once neostigmine therapy has been introduced.

There is likewise suggestive evidence that the likelihood of remission following thymectomy is less if the patient has been on neostigmine treatment for more than a short period of time. As an example, one may consider the course of two male patients of the same age who had the disease for a comparable length of time and from each of whom a thymoma of approximately the same size and cellular composition was removed. One man took neostigmine in large amounts for over two years preoperatively, while the other received antisyphilitic treatment because the thymoma was considered to be an aneurysm and the correct diagnosis was not made until the day before operation. The untreated patient promptly recovered following thymectomy while the other had no relief of symptoms and died a year later.

The mortality associated with the operation is low if the postoperative care is in the hands of clinicians experienced in the handling of patients with this disease. The chance for recovery from myasthenia gravis after operation is greater if thymectomy is performed early in the course of the disease; indeed, it may be equal or better than the chance that the disease will remain so mild that it can be easily controlled by the therapeutic methods available and will allow the patient to lead a relatively normal life. Serious consideration must be given by those clinics having facilities to handle patients with this disease to the view that thymectomy may be the treatment of choice if done as soon as the diagnosis of myasthenia gravis is made. Further results in a series of cases operated upon at this stage, regardless of the severity of the symptoms, may also clarify the relationship of the thymus to this disease and furnish clues to the normal physiological function of this mysterious organ.

A. McGehee Harvey, M.D.

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Clinical Studies

Antibacterial Precipitating Antibodies in Group A Hemolytic Streptococcus Sore Throat*

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INTEREST in hemolytic streptococcal disease has been enhanced during the last decade as the result of the presentation of evidence[1] that rheumatic fever is a sequel to infection by these organisms and by the appearance of new information[2] in regard to the nature of the infectious agent. Hemolytic streptococcal infections in man, particularly of the respiratory tract, are caused by members of a single serological group designated by the letter "A," the members of which may be segregated into types by agglutination or precipitation technics.[2]

Strains of Group A elaborate a number of filterable substances such as the erythrogenic toxin, hemolysin and the serum protease activator usually known as fibrinolysin. A neutralizing antibody for each of these often appears during convalescence in the serum of human beings who have been infected by Group A streptococci. Extensive studies have been made of these antibodies with special reference to the rheumatic state as well as glomerulonephritis.[3–8]

Antibacterial antibodies have attracted less attention and have not been studied in comparable detail. Various antigens and technics have been used for the purpose of detecting immune substances in human sera capable of reacting with streptococcal cells or certain of their constituents.

Precipitin tests have been made using streptococcal protein, soluble at neutrality or in alkaline solutions (nucleoprotein)[6,9–12] protein soluble in acid, sometimes purified by precipitation with alcohol ("M" extracts with or without "C" carbohydrate,[13–20] purified "C" carbohydrate[6,11]) or extracts of the whole ground organism.[12] Earlier investigators studied the agglutination of hemolytic streptococci by human sera in an attempt to establish the etiology of certain disorders such as scarlet fever.[22] More recently others have described the presence of agglutinating antibodies in several human disease states and during convalescence from hemolytic streptococcal infection.[16,18,20,23–26]

Antibacterial antistreptococcal antibodies have been detected less frequently by animal protection tests[27] or by technices involving the inhibition of growth of the living organism by whole blood containing phagocytes.[28]

Many of the studies mentioned above were carried out in groups of patients suffering from rheumatoid arthritis. Precipi-

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tating or agglutinating antibodies were invariably discovered in the sera of a high percentage of such individuals, regardless of the nature of the extract or whole organisms used as an antigen in the test. The significance of these observations has never been determined. The presence of such antibodies may be an example of non-specific production of immune substances similar to the Well-Felix reaction, or it may indicate an intimate relationship between the disease and some variety of streptococcus. Further discussion of this problem will not be attempted in this paper.

As information in regard to the antigenic structure of the hemolytic streptococcus has accumulated, attempts have been made to demonstrate the presence or development of antibodies reacting with specific fractions. Most important are the studies of Coburn and Pauli[18] and Swift and Hodge,[14] who observed precipitating antibodies against purified acid extracts of Group A streptococci in streptococcal disease and rheumatic fever. These investigators have stated that there was a delayed development of such antibodies when a hemolytic streptococcal respiratory infection was followed by the appearance of some manifestation of the rheumatic state. In both instances it was originally believed that the antibody under study was reacting with the type specific "M" protein in the extract, but it has since become apparent that this was not usually the case,[20,29] since extracts from streptococci of a single type will induce precipitation with the sera of patients who are convalescing from an infection caused by organisms of several types. Similar non-type specificity has also been demonstrated for agglutinating antibodies.[20,26]

A systematic study of the development of antibacterial antibodies in a large number of human beings infected by Group A hemolytic streptococci has rarely been undertaken.[5] A homogenous, closely controlled group has never been investigated under circumstances permitting the correlation of the antibody phenomena with the natural history of streptococcal respiratory disease.

It is the purpose of this paper to characterize certain antigens derived from Group A hemolytic streptococci and to describe the results of their use in precipitin tests in a large number of young adults who had suffered from infection by hemolytic streptococci.

MATERIALS AND METHODS

The Precipitin Test. Organisms: The hemolytic streptococci used in the preparation of precipitating antigens were isolated from the respiratory tract of infected human beings and grouped and typed by the serological methods of Lancefield.*[30,31] The strains were in the matt phase when the extracts were prepared, and they yielded large amounts of the acid-soluble type-specific "M" substance.

Antigens: The technics used in the preparation of the antigens for the precipitin test will be described in another section.

The Test: The precipitin tests were carried out in a manner similar to that described for typing hemolytic streptococci.[31] The serum to be studied was drawn into sterile, thin-walled capillary tubes of 1.0 to 1.5 mm. in diameter followed by a similar amount of the sterile antigen solution. Great care must be exercised to obtain serum from under the fat layer if possible and to be certain that the serum and antigen are in contact without an intervening air bubble. It is essential that a saline con-

* Group specific sera were prepared by the Lederle Laboratories and type specific sera by Squibb & Co. These sera were also used during other phases of the study for the detection and quantitative estimation of "M" protein and "C" carbohydrate.

trol be run with each serum. After filling, the small tubes were placed in plasticine in racks with the serum above the antigen solution.

The racks of tubes were incubated for twenty-four hours circa 36°C. and placed in the cold room for one week. The temperature was maintained circa 2°C. During the prolonged period of refrigeration a precipitate formed if the antibody was present and settled to the bottom of each tube where it could be easily seen and described. Saline controls were rarely positive. The results were recorded as follows: Negative—no, or very small amounts of precipitate; positive—definite precipitate, usually forming a column in the tube 0.5 mm. or more in height. This technic, which required small amounts of serum and extract, was very satisfactory and the results were entirely reproducible.

CLINICAL MATERIAL

The human sera used in the immunological studies to be described in this paper were collected during an intensive study of the natural history of Group A hemolytic streptococcal sore throats in young men. The nature of the group and the clinical and bacteriological information obtained have been fully described in a series of reports.[1,32–37] Clinical, clinicopathological and immunological data were available for 335 cases of streptococcal infection selected on clinical and bacteriological grounds. Definite infection was established in approximately 80 per cent of the patients by the development of a significant increase of the antistreptolysin titer during convalescence. Many of the other patients undoubtedly were, but cannot be proved to have been, infected. Some of these were examples of a non-streptococcal respiratory disease which occurred in an individual who was previously a Group A hemolytic streptococcal pharyngeal carrier.

CHARACTERIZATION OF THE ANTIGENS

Two antigens extracted from Group A hemolytic streptococcus cells were used in this study. They will be briefly characterized.

The "X" Antigen. Previous investigators have demonstrated that acid extracts of Group A hemolytic streptococcal cells contain a substance that will form precipitate with an antibody; this develops in the serum of human beings convalescent from an infection from these organisms and also in certain other pathological states. It was originally believed that the reaction occurred between the type-specific "M" substance and type-specific antibody, but more recent observations have indicated that this is not the case.

The nature of this antigen (hereafter called the "x" antigen) has been extensively studied in this laboratory. The work is not complete but certain essential details may be summarized. A full report will be presented elsewhere.

"x" antigen is regularly present in acid extracts of matt strains of Group A streptococcal cells of all types that have been examined. It is well preserved after removal of the group carbohydrate "c" by alcohol precipitation. The purified antigens prepared from strains of five types induced precipitation regularly with human sera collected during convalescence from infection with several types.

"x" antigen could not be detected if the extract were diluted 1:50 although "M" substance formed excellent precipitates with specific animal sera at dilutions of 1:1000. Various dilutions of the extracts were made between 1:50 and 1:500 and used in tests with sera obtained from patients convalescent from infection by streptococci of the homologous type. The presence of type-specific antibody was never demonstrated. These observations show that the reaction is not related to the M-anti-M antibody system.

Fractional alcohol precipitation was undertaken at various temperatures for the purpose of separating the type and group specific antigens present in the purified acid extract. This was never accomplished. All fractions in which an increased concentration of "M" substance was detected also contained a comparably increased amount of "X" antigen.

The anti-X antibody could be readily removed by adsorption to heat killed matt (M rich) and trypsin treated (M free) Group A hemolytic streptococcus cells but not to cells of E. coli or Staph. aureus. More detailed studies of this type are in progress.

The antigen used in the tests described in this paper was prepared as follows:

(1) Matt type 17 hemolytic streptococci, derived from 100 liters of veal infusion neopeptone broth, were extracted and purified by the method of Lancefield;[39] (2) the resulting material was precipitated in the presence of 3 volumes of 95 per cent ethyl alcohol and the precipitate recovered in 40 ml. of normal salt solution; (3) one volume of 95 per cent ethyl alcohol was added to the material, the precipitate removed in the centrifuge and discarded; (4) two additional volumes of alcohol were added to the supernatent obtained during step three. The resulting precipitate was recovered in 40 ml. of normal saline, preserved with merthiolate in a concentration of 1:10,000 and used for the tests.

Steps three and four were carried out throughout at the temperature of melting ice.

Precipitation did not occur when this material was tested in various dilutions against an animal serum containing large amounts of anti-C antibody. At a dilution of 1:1,000 it formed large amounts of precipitate with a type-specific anti-M serum prepared against a strain of type 17. At a dilution of 1:16, it reacted strongly with the non-type-specific anti-X antibody present in the sera of human beings convalescent from infection by Group A hemolytic streptococci.

The "C" Antigen. The group specific "C" carbohydrate used for the tests to be described was obtained from Group A hemolytic streptococcal cells in a purified form by the method of Fuller.[40] The resulting fine, white powder was dissolved in normal salt solution of a concentration of .025 mg. per ml. for use in the tests.

SUMMARY

A substance is present in "M"-rich acid extracts of Group A hemolytic streptococcus cells which is not type-specific and is not the group specific "C" carbohydrate. This material forms precipitates with an antibody present in the serum of patients convalescent from infection by Group A streptococci. An extract containing this substance was prepared and used in association with a solution of purified "C" carbohydrate in a microprecipitin technic for the detection of antibodies in human sera.

ANTIBODY PHENOMENA

Presence of Antibody at Onset of Infection. Antibodies reacting with the "X" and "C" antigens were present in the sera from certain cases at the onset of the acute streptococcal illness. The former were detected in forty-five or 13.8 per cent, and the latter in forty-two, or 12.8 per cent, of 327 acute phase sera that were studied. These antibodies were present simultaneously in twenty-one cases. The antistreptolysin* titers[38] of these sera were correlated with the presence or absence of the precipitating antibody. The derived data are summarized in Table I.

The antistreptolysin titer was 100 units per ml. or less, in 61.7 per cent of those

* The antibody studied was antistreptolysin "O".

TABLE I

CORRELATION OF ANTISTREPTOLYSIN TITERS AND PRECIPITIN TITERS OF ACUTE PHASE SERA

Precipitin Reaction	No.	Antistreptolysin titer in units per cc.											Titer 100 units or less		Titer 125 to 250 units		Titer 333 units or more	
		12	50	100	125	166	250	333	500	625	833	1,250	No.	%	No.	%	No.	%
X and C positive	21	0	1	3	6	6	2	0	1	1	0	1	4	19.0	14	66.6	3	14.3
X only positive	24	2	6	8	1	3	3	1	0	0	0	0	16	66.6	7	29.2	1	4.2
C only positive	21	3	5	3	8	2	0	0	0	0	0	0	11	52.4	10	47.6	0	0.0
X and C negative	256	52	65	41	43	37	12	2	2	2	0	1	158	61.7	92	35.7	6	2.3

sera in which no precipitating antibody was detected. In only 2.3 per cent was the antibody level greater than 250 units per ml. Comparable values were obtained when sera containing either x or c precipitin were studied. If both x and c precipitins were present, the results were different in that the antistreptolysin titer was 100 units per ml. or less, in 19.0 per cent and was greater than 250 units per ml. in 14.3 per cent. These are statistically significant variations.

A significant antistreptolysin response occurred in 54.5 per cent of those patients in which anti-x antibody was present and in 53.6 per cent of those in which anti-c antibody were present in the initial serum. (Table v.) This is a lower frequency of response than was observed among the group in which these antibodies were absent.

There was no relationship between the presence of either precipitin at the onset of acute streptococcal infection and the presence or absence of a positive Dick skin test.

Data presented in Tables II and IV demonstrate that, if either antibody was present in the initial sera, it was also present in sera obtained during the fourth week of the disease or later in nearly every case. By this time c antibody had disappeared in one and x antibody in five individuals.

One hundred forty-six acute phase sera were obtained from patients suffering from non-streptococcal respiratory infections. Anti-x antibody was demonstrable in twenty-nine, or 19.8 per cent, of these, and anti-c antibody in thirty, or 20.0 per cent. The two antibodies occurred simultaneously in sixteen patients. These values are all slightly higher than those derived from the study of the streptococcal disease just described but the differences are not statistically significant.

Antibody Response. Serial determinations of the anti-x and anti-c antibodies were made in 278 cases of hemolytic streptococcus sore throat at intervals which permitted a comparative description of antibody response in these cases. Sera were collected on the second or third days of the acute illness, again between the eighth and tenth days and during the fourth week (twenty-one to thirty days). A smaller group was studied for a longer period. The essential data are summarized in Table II. There were, in addition, a number of patients in which the follow-up examination was not obtained until after the thirtieth day. These will be considered separately.

Neither antibody was initially present in 214 patients. When these men were re-examined during the fourth week, anti-x antibody had appeared in forty; anti-c in thirteen and both antibodies in fourteen. Anti-x, but not anti-c, antibody was

detected on the first examination in the sera of nineteen patients, in five of whom an anti-C response had occurred by the fourth week. Anti-X antibody disappeared in two cases. An anti-X antibody response was observed in six of seventeen cases in which anti-C antibody had been initially present.

situation prevailed in regard to the anti-C antibody in two cases. In both, antibody was still present during the sixth week.

The follow-up serum was obtained after the thirtieth day in certain patients. The data derived from a study of these patients are presented in Table III. Anti-X antibody

TABLE II

ANTI-X AND ANTI-C ANTIBODY RESPONSE IN 278 PERSONS INFECTED BY HEMOLYTIC STREPTOCOCCI

	Initial Serum																Initial Serum											
	Anti-X and anti-C antibody absent,					Anti-X antibody present. Anti-C antibody absent,				Anti-C antibody present. Anti-X antibody absent,				Anti-X and anti-C antibodies, present,				Anti-X antibody absent; all cases						Anti-C antibody absent; all cases					
	4th week serum					4th week serum				4th week serum				4th week serum															
Total Cases	Total cases	X and C antibody absent	X antibody present	C antibody present	X and C antibody present	Total cases	X antibody absent	X antibody present C antibody absent	X and C antibody present	Total cases	C antibody absent	C antibody present X antibody absent	C and X antibody present	Total cases	X antibody absent	X and C antibody present	Total cases	X antibody present on day 8 to 10		X antibody present on day 21 to 30		X antibody response absent		Total cases	C antibody present on day 8 to 10		C antibody present on day 21 to 30		C antibody response absent	
																		No.	%	No.	%	No.	%		No.	%	No.	%	No.	%
278	214	147	40	13	14	19	2	12	5	17	1	10	6	18	3	15	231	10	4.3	60	26.0	171	74.0	233	6	2.6	18	7.7	215	92.3

There was a total of 231 patients in whom anti-X antibody was not discovered early in the disease. This antibody had appeared by the tenth day in ten, or 4.3 per cent, and by the fourth week in sixty, or 26.0 per cent. Anti-C antibody was not present in the initial serum from 233 patients. It had developed by the tenth day in six, or 2.6 per cent, and by the fourth week in eighteen, or 7.7 per cent.

Anti-X antibody was absent in the initial serum but present by the tenth day in six additional patients in whom the follow-up study was not done until the fifth to seventh weeks. At that time, four were still positive and two had become negative. A similar

developed in seven, or 20.0 per cent of thirty-four patients in this group in whom it was initially absent. The results of the study of anti-C antibody were similar except that an immune response occurred in five, or 12.8 per cent of thirty-nine patients.

Serial studies were available after the fourth week in twenty-seven patients in whom the anti-X, and in thirty-nine patients in whom the anti-C substances had not appeared within the first thirty days after the onset of the acute streptococcal disease. The data are presented in Table IV. Antibodies developed in four of each group although the studies were continued in several cases for more than fifty days.

Persistence of these antibodies was also studied in certain patients in whom these substances were initially present or developed during the first four weeks (Table IV). Anti-x antibody disappeared from the serum of two of a group of twenty-six patients, thirteen of whom were followed for more than forty-five days and nine for more than seventy days. Anti-c antibody persisted in all of fourteen cases in whom observations were available after the fourth week.

The presence of these antibodies clearly does not confer resistance against infection by Group A hemolytic streptococci, since they were initially demonstrable, either separately or together, in many men in whom an antistreptolysin response occurred, indicating that definite tissue invasion by these organisms had taken place. The frequency of antistreptolysin response was less in the men in whom these antibacterial antibodies were present at the onset of the acute illness, suggesting that a certain

TABLE III

ANTI-X AND ANTI-C ANTIBODY RESPONSE IN PATIENTS WITH LATE FOLLOW-UP ONLY

Initial Serum	Total Cases	Day of follow-up examination													
		31–35		36–40		41–45		46–50		51–60		61–70		71 and over	
		+	−	+	−	+	−	+	−	+	−	+	−	+	−
X antibody absent	34	3	16	2	2	1	3	1	2	..	3	..	..	..	1
C antibody absent	39	3	19	1	5	..	3	1	4	..	3				

The development of precipitins has been compared with the frequency of significant antistreptolysin response. The data are presented in Table V. An increase in the latter antibody occurred in a comparable number of cases whether anti-x or anti-c precipitins did, or did not, appear during convalescence.

COMMENT

As a result of the studies just described, it is possible to state that antibacterial antibodies, reacting with the "x" antigen and the "c" carbohydrate, were present in the sera of many men of military age at the onset of hemolytic streptococcal infection. These were not the non-specific precipitins of the type described by Tillet and Francis,[41] since they persisted into convalescence in nearly every instance in which observations were available at an appropriate time.

number of these cases were not actually instances of streptococcal respiratory disease. If this interpretation is correct, the hemolytic streptococci isolated from the throat and the antibodies discovered in the serum were the late results of a previous streptococcal infection.

Anti-x precipitins developed in approximately one-quarter, and anti-c precipitins in about 8 per cent of the members of this group of men infected by Group A hemolytic streptococci in whom these antibodies were not present at the onset of the illness. An antibody response had occurred in a few cases by the tenth day and was maximal by the end of the fourth week.

A small group of patients in whom precipitins had not appeared by the fourth week were followed for a longer period. The detection of only a few additional responses was accomplished by this procedure.

TABLE IV

LATE DEVELOPMENT OR PERSISTENCE OF ANTIBACTERIAL ANTIBODIES IN PATIENTS WITH PROLONGED FOLLOWUP STUDY

(Each patient recorded only once)

Initial Serum	Fourth Week Serum	Day of Followup Examination *													
		31–35		36–40		41–45		46–50		51–60		61–70		71 and over	
		+	−	+	−	+	−	+	−	+	−	+	−	+	−
Anti-x Antibody															
Anti-X antibody absent	Anti-X antibody absent *	2	8	1	4	1	3	..	2	..	4	..	..	..	2
Anti-X antibody absent	Anti-X antibody present †	3	..	3	1	3	1	1	..	..	1	..	..	3	
Anti-X antibody present	Anti-X antibody present †	1	..	..	..	1	..	1	..	..	..	1	..	6	
Anti-c Antibody															
Anti-C antibody absent	Anti-C antibody absent *	1	10	..	6	1	3	..	3	1	4	1	2	..	7
Anti-C antibody absent	Anti-C antibody present †	2	..	2	..	3	..	..	..	..	..	..	..	4	
Anti-C antibody present	Anti-C antibody present †	1	..	1	..	..	..	..	..	..	..	..	..	1	

* Last negative or earliest positive test recorded.
† Last positive or earliest negative test recorded.

Actual infection by hemolytic streptococci occurred in the men in whom no precipitins developed, since the frequency of significant antistreptolysin response in this group was similar to that observed in those cases in which either anti-x or c antibody developed.

The duration of the follow-up study was insufficient to determine the total length of time that anti-x and anti-c antibodies might persist in the serum when initially present or after their appearance as the result of infection. These antibodies disappeared in only two of a small group of patients who were studied from forty-five to seventy days after the acute illness.

RELATIONSHIP OF ANTIBODY PHENOMENA TO NATURE OF DISEASE

The relationship of the initial presence or the later development of the anti-x and anti-c antibodies to the nature and course of hemolytic streptococcus sore throat has been evaluated and the results presented below.

Acute Illness. The maximum recorded temperature, duration of fever, total leukocyte count, initial and follow-up (fourth week) and erythrocyte sedimentation rates (Westergren) were compared with the presence or absence of anti-x or anti-c precipitins at the onset of the disease. Information was available in 335 cases of Group A streptococcal respiratory disease. This analysis failed to reveal a correlation in any category of clinical or laboratory signs between the presence or absence of these antibodies and the nature or course of the acute suppurative phase of the illness. The data on which this statement is based have not been presented in this paper.

TABLE V

COMPARISON OF THE FREQUENCY OF SIGNIFICANT ANTISTREPTOLYSIN RESPONSE WITH THE PRESENCE OR DEVELOPMENT OF ANTI-X OR ANTI-C PRECIPITINS

Initial Serum	Followup Serum	Number of Cases	Significant Antistreptolysin Response	
			Number	Per Cent
X antibody absent	X antibody absent	172	136	79.1
X antibody absent	X antibody present	75	62	82.7
X antibody present	X antibody present	44	24	54.5
C antibody absent	C antibody absent	237	191	80.6
C antibody absent	C antibody present	40	31	77.5
C antibody present	C antibody present	41	22	53.6

TABLE VI

RELATIONSHIP OF SUPPURATIVE COMPLICATIONS TO PRESENCE OR DEVELOPMENT OF ANTI-X OR ANTI-C ANTIBODIES

	Suppurative Complications		All Cases	
	No.	Per Cent	No.	Per Cent
X Antibody				
Total	29	100.0	298	100.0
Always absent	21	72.4	196	65.7
Present initially	3	10.3	37	12.4
Developed during convalescence	5	17.2	65	21.8
C Antibody				
Total	29	100.0	298	100.0
Always absent	24	82.8	244	81.9
Present initially	2	8.3	35	11.7
Developed during convalescence	3	10.3	19	6.4

Cases in which anti-x and anti-c antibody developed during convalescence were also studied to determine whether the appearance of these antibodies was related to the severity of the acute disease as measured by the clinical and laboratory information just described. No correlation in any category was discovered between antibody response and the nature of the initial illness.

Suppurative Complications. Twenty-nine of the cases in whom suitable serial precipitin determinations were available had suffered from a definite suppurative complication of hemolytic streptococcal sore throat.[35] The initial disability in these patients was prolonged and accentuated as a result of otitis media, peritonsillar abscess or sinusitis. In spite of this fact, examination of Table VI reveals that anti-x and anti-c antibodies were present at the onset of the disease or developed during convalescence with the same frequency among these cases as in the group as a whole.

Non-suppurative Complications. A considerable number of hemolytic streptococcal respiratory infections in this study group initiated pathological processes, apparently of a non-suppurative nature. Clinical manifestations of these disorders were arthritis with or without fever, or carditis (rheumatic fever), late fever with or without carditis, carditis without fever or arthritis and pneumonitis with or without carditis.[36] All of these syndromes may well have a common pathogenesis.[1] The data derived from a study of these cases have been analyzed in relation to the presence or development of precipitating antibodies to determine whether the presence or absence of these substances might be related to the appearance of these complications. Other post-streptococcal phenomena, perhaps less clearly allied to these disorders, such as late adenitis, have been omitted.

The essential data are presented in Table VII. The total number of cases is larger than that described in Table II since patients were included for the purpose of this analysis in whom the first follow-up observation was not made until after the fourth week. (Table III.)

TABLE VII

RELATIONSHIP BETWEEN THE INITIAL PRESENCE OR LATER DEVELOPMENT OF ANTI-X AND ANTI-C ANTIBODIES AND THE FREQUENCY OF OCCURRENCE OF NONSUPPURATIVE POSTSTREPTOCOCCAL COMPLICATIONS

	Complications		Antibody Status									Antibody Status								
			X Antibody Never Present			X Antibody Present Initially			X Antibody Developed during Convalescence			C Antibody Never Present			C Antibody Present Initially			C Antibody Developed during Convalescence		
	No. of Cases	Per Cent of All Cases	No. of Cases	Per Cent Total in This Antibody Category	Per Cent of Complication	No. of Cases	Per Cent Total in This Antibody Category	Per Cent of Complication	No. of Cases	Per Cent Total in This Antibody Category	Per Cent of Complication	No. of Cases	Per Cent Total in This Antibody Category	Per Cent of Complication	No. of Cases	Per Cent Total in This Antibody Category	Cent of Complication	No. of Cases	Per Cent Total in This Antibody Category	Per Cent of Complication
Arthritis	18	6.0	3	1.5	16.7	7	18.9	38.9	8	12.3	44.4	10	4.1	55.6	3	8.6	16.7	5	26.3	27.7
Late fever	13	4.4	11	5.6	84.5	0	0.0	0.0	2	3.1	15.5	13	5.3	100.0	0	0.0	0.0	0	0.0	0.0
Carditis, all cases	16	5.4	9	4.6	56.2	1	2.7	6.2	6	9.2	37.5	11	4.5	68.7	4	11.4	25.0	1	5.3	6.3
Carditis with late fever	6	2.0	5	2.6	83.4	0	0.0	0.0	1	1.5	16.6	6	2.5	100.0	0	0.0	0.0	0	0.0	0.0
Carditis without late fever	10	3.4	4	2.0	40.0	1	2.7	10.0	5	7.7	50.0	5	2.0	50.0	4	11.4	40.0	1	5.3	10.0
Pneumonitis	3	1.0	0	0.0	0.0	0	0.0	0.0	3	4.6	100.0	2	0.8	66.3	0	0.0	0.0	1	5.3	33.3
All complications	44	14.8	18	9.1	40.9	8	21.6	18.2	18	27.7	40.9	30	12.3	63.4	7	20.0	15.8	7	36.8	15.8
Total uncomplicated	254	85.2	178	90.9	70.0	29	78.4	11.4	47	72.3	18.6	214	87.7	84.3	28	80.0	11.0	12	63.2	4.7
Total cases	298	100.0	196		65.7*	37		12.4*	65		21.8*	244		81.9*	35		11.7*	19		6.4

* Per cent of total cases.
(Read columns headed "% total in this antibody category" vertically.)
(Read columns headed "Per cent of complication" horizontally.)

Arthritis. Arthritis of varying degrees of severity followed the initial hemolytic streptococcus sore throat in eighteen, or 6.0 per cent of all cases. x antibody was never demonstrated in the sera of three (Cases 3, 4, and 11[36]); it was present at the onset of the acute sore throat in seven (Cases 2, 7, 8, 12, 13, 16, and 17[36]) and it appeared during convalescence from the initiating streptococcal infection in eight (Cases 5, 6, 9, 10, 14, 15, 18, 19[36]). This antibody was either initially present or developed later in 83.3 per cent of the patients with an involvement of the joints. Anti-x precipitin was discovered early or during convalescence in only 30.0 per cent of the uncomplicated and in 34.2 per cent of all the patients.

If each antibody category is considered, 1.5 per cent of those in whom anti-x antibody was never present, 18.9 per cent of those in whom it was detected in the initial serum and 12.3 per cent of those in whom it appeared later developed arthritis. This complication occurred ten times as frequently when anti-x antibody was present early or appeared later. The differences just described are statistically significant. It was previously noted that an antistreptolysin response occurred less frequently in those patients in whom the x antibody was initially present. Thirty-five per cent of this group in whom infection by streptococci could be established by the appearance of increased amounts of antistreptolysin developed arthritis.

If the anti-x precipitin appeared during convalescence from the acute respiratory illness, it was invariably demonstrable at the end of the third, or early in the fourth week and was always present at the time when arthritis became manifest. The three patients in whom this precipitin was never discovered were followed for fifty-seven, seventy-four and 132 days until recovery from the arthritic process which was severe or moderately severe in all. The possibility of a late antibody response in these patients has been excluded.

When the anti-x antibody had appeared in these arthritic patients it persisted in fourteen of fifteen patients throughout the period of observation which varied from thirty-nine to 160 days, with a mean of eighty-five days, after the onset of the initiating streptococcal disease. Disappearance of the antibody was noted in one case between the forty-ninth and fifty-seventh days.

Table VII also demonstrates the frequent occurrence of anti-c precipitins either initially or during convalescence in post-streptococcal arthritis. It will be noted that there were ten cases in which this antibody was always absent. x antibody was demonstrated in seven of the remaining eight. This is a more frequent simultaneous occurrence of the two antibodies than for the whole group (65 per cent of all cases in which anti-c antibody was demonstrated) but the difference may be the result of the statistical errors of small groups.

Late Fever. A febrile illness which followed hemolytic streptococcus sore throat after a latent or quiescent period of five to nineteen days in length and often associated with electrocardiographic evidence of carditis was frequently observed during this study.[36] It has been regarded as a disorder similar in pathogenesis to the arthritic disease just discussed.

The data in Table VII reveal that, from an immunological standpoint, the two disorders are very different. Anti-x precipitins were rarely (15.5 per cent) and anti-c precipitins at no time demonstrated in the sera of patients in whom late fever supervened. Electrocardiographic evidence of carditis was detected in six of these patients, in one of which anti-x precipitin was present at the onset of the acute streptococcal disease.

Carditis. Carditis with late fever has just been described. In addition, abnormal electrocardiograms were discovered in ten cases during convalescence from the initial streptococcal infection in the absence of arthritis or late fever. Anti-x antibody was detected in the serum obtained at the onset of the acute respiratory infection in one and appeared during convalescence in five other cases. The frequency of occurrence of this precipitin in these individuals is greater than that for the whole group but the differences are not statistically significant and are not comparable with those observed when arthritis was present. It may be worth while to note that electrocardiographic evidences of carditis were not marked and the duration of carditis was short in three (Cases 3, 15 and 20[33]) of the four cases in which x-antibodies were never detected. Anti-c antibodies were demonstrable in the initial serum of four and developed during convalescence in one of these examples of poststreptococcal carditis. There was an associated occurrence of anti-x antibody in four of these cases. This situation, therefore, closely parallels that observed in the arthritic group.

Pneumonitis. A pneumonitis believed to have been non-suppurative complicated the course of three cases of streptococcal sore throat.[36] Anti-x antibody developed during convalescence from the initial illness in all of these individuals.

COMMENT

The observations just described have demonstrated that there was no correlation between the nature or severity of the acute suppurative phase of hemolytic streptococcus sore throat and the presence of antibacterial precipitating antibodies at the onset of the disease or their appearance during convalescence.

A striking relationship was discovered between the occurrence of these antibodies and the development of the late non-suppurative complications of the poststreptococcal state. The anti-x precipitin was demonstrable in the sera obtained at the onset of the streptococcal respiratory disease or in those obtained during convalescence from it in fifteen, or 83.3 per cent of eighteen cases of poststreptococcal arthritis. A similar correlation was observed between the presence of this antibody and of poststreptococcal non-suppurative pneumonitis. An analogous but less definite relationship was observed with regard to non-febrile poststreptococcal carditis. Anti-x antibody was rarely demonstrated at any time during the course of hemolytic streptococcus sore throat complicated by a late, presumably non-suppurative, febrile illness with or without carditis.

Previous investigators[14,18] believed that a precipitin, apparently the same as that described as the x antigen in this paper, was delayed in its development if arthritis supervened following hemolytic streptococcal respiratory disease. This was not the case in this group.

GENERAL DISCUSSION

The results of many investigations[1] have established the fact that there is an intimate relationship between Group A hemolytic streptococcal disease, particularly of the upper respiratory tract, and the rheumatic state. It was demonstrated in a recent critical study[1] that arthritis was a sequel to respiratory infection only when the etiological agent of the initiating disorder was the hemolytic streptococcus and that a non-arthritic, continuing pathological process with or without carditis often followed diseases caused by these organisms.

Considerable indirect evidence indicates that these serious late non-suppurative complications of hemolytic streptococcal infection are the result of an immunological process, probably analogous to serum sick-

ness. The suggestion has been made that sensitization of human beings occurs as the result of exposure to some fraction or product of hemolytic streptococci and that this substance must be common to all or, at least, to many different types or strains of Group A hemolytic streptococci because complications follow infection or reinfection by different strains or types of these organisms.[1]

Among the known possible sensitizing proteins elaborated by Group A streptococci are the erythrogenic toxin, the serum protease activating substance usually called fibrinolysin, streptolysins "O" and "S," the "X" substance described in this paper, the "C" carbohydrate as it occurs in antigenic combination with protein in the bacterial cell and the various nucleoproteins of Heidelberger.[10] The "M" and "T" substances would not seem suitable since they are type specific and dissimilar in different strains. For reasons to be detailed elsewhere, it is probable that the four "exotoxins" just listed are not involved in the pathogenesis of the poststreptococcal state.

This paper describes a study of two substances extracted from the streptococcal cell, both of which are group rather than type specific, and which might therefore be sensitizing agents capable of inciting the phenomena of the poststreptococcal state. One was the well known "C" carbohydrate; the other, the "X" substance is present in acid extracts of Group A streptococcal cells and forms non-type-specific precipitates with sera obtained from certain normal human beings and from others convalescent from hemolytic streptococcal infection. The nature of this antigen is, as yet, undefined. It is closely associated with the type specific "M" substance from which it has not been possible to separate it by chemical methods, and may well be the "nucleoprotein" which has been described by Zittle in "M" extracts.[42]

If the pathogenesis of these disorders is the result of an immunological reaction of the anaphylactic type, it is reasonable to suppose that a circulating antibody might be present in serum obtained from affected persons which would be capable of reacting with the sensitizing antigen, as is the case in serum sickness.[43] The present investigation is the result of a search for such an immune substance.

Antibodies reacting with the "C" carbohydrate or "X" protein were present in approximately 15 per cent of cases of acute streptococcal respiratory disease at the onset of the illness and cannot be regarded as conferring protection against tissue invasion by these organisms. Anti-x precipitin appeared during convalescence in the sera of approximately 22 per cent, and anti-c precipitin in approximately 6 per cent of the remaining patients. Antibody response was nearly maximal by the end of the fourth week.

The nature and severity of the acute suppurative phase of hemolytic streptococcal sore throat was not altered by the initial presence or later development of either of these antibodies. A different situation prevailed in regard to non-suppurative complications. Anti-x antibody was present at the onset of the sore throat or later in fifteen of eighteen individuals in whom arthritis was a sequel to hemolytic streptococcal respiratory disease; 14.7 per cent of cases in whom this precipitin was at some time demonstrated developed involvement of the joints; only 1.5 per cent of those in whom it was not demonstrated did so. These differences are of statistical significance and there can be no doubt that the presence of this antibody is, in some way, related to the rheumatic state. Additional studies not reported here of sera obtained from other cases of rheumatic fever in military personnel, in whom the initiating streptococcal infection had not been ob-

served, confirm this fact.[44] An anti-x antibody response also occurred in all of three cases of non-suppurative poststreptococcal pneumonitis.

A similar but less striking correlation was discovered between the presence of x antibody and afebrile poststreptococcal carditis. The precipitin was rarely demonstrated in sera from patients in whom poststreptococcal fever occurred. The arthritic and non-arthritic poststreptococcal disorders have been previously regarded as of a similar pathogenesis although clinical study showed that involvement of the joints was associated with a more severe process. Definite evidence is presented here which establishes an immunological difference between the two syndromes.

Anti-c antibody was not discovered more frequently in complicated than in uncomplicated streptococcal disease except in a few arthritic cases in which it occurred in association with the x antibody. It is not believed to be related to poststreptococcal non-suppurative disease.

Discussion of the manner in which the x antigen may be involved in the pathogenesis of poststreptococcal arthritis must be speculative. It is possible that this substance is the sensitizing antigen and that its antibody is responsible for the development of the rheumatic state.

If the x substance is not the sensitizing agent, the presence of its antibody in these cases may merely mirror a general increase of immunological response on the part of these human beings to streptococcal products which places them in a group in which arthritis caused by hypersensitivity phenomena is more likely to appear following streptococcal infection. This hypothesis becomes less tenable when it is known that these same individuals did not produce antistreptolysin or antifibrinolysin in unusually large amounts[45,46] as the result of the initiating hemolytic streptococcus infection.

It is also possible that the development of anti-x antibody is related in some nonspecific way to disease of the joints since it, or a closely related precipitin, is often demonstrable in the serum of patients suffering from rheumatoid arthritis, a disease whose pathogenesis may be different from that operative in poststreptococcal arthritis.

The validity of any of these hypotheses cannot be determined at the present time. The first is most attractive and opens more promising avenues for future investigation.

The absence of the anti-x antibody from the sera of patients suffering from poststreptococcal fever is disturbing, since this syndrome was believed[1] to be the result of a pathological and immunological process similar to that causing the arthritic disease. This point of view may not be correct, but it is also possible that differences noted are quantitative rather than qualitative. The suggestion has already been made on the basis of bacteriological and clinical information[1,36] that arthritic poststreptococcal disease was associated with a greater degree of hypersensitivity requiring repeated infection by hemolytic streptococci in certain patients. The absence of anti-x antibody in many poststreptococcal fevers may indicate that the reaction in these individuals was insufficiently violent to produce a measurable excess of antibody in the circulating blood. This would be in approximate accord with observations in horse serum sickness[43] in which large amounts of anti-horse serum precipitin appeared when the disease was severe and small amounts or none when it was mild.

An important difference exists between the phenomena described here and those previously reported in serum sickness.[43] Anti-horse serum precipitins were not demonstrable until the clinical manifesta-

tions of the immunological disorder had abated although the sensitizing antibody must have been present for a much longer time. Precipitin was not measurable in the circulating blood until the huge quantity of antigen (horse serum) had been either immunologically neutralized, metabolized or excreted. Excess sensitizing antibody might be expected to appear earlier in the serum of human beings infected with hemolytic streptococci since the amount of antigen capable of neutralizing antibody *in vivo* is much smaller than in serum disease.

Earlier investigators have stated that the production of anti-x antibody or a closely related substance was delayed following hemolytic streptococcus sore throat if rheumatic fever was a complication.[14,18] This observation has not been confirmed by the present study. The reason for this discrepancy is not apparent but it is possible that the method was capable of detecting antibody in smaller amounts than the technic used by other workers.

Another detailed investigation[5] of precipitating antistreptococcal antibodies failed to reveal any significant differences between the occurrence of these substances in streptococcal respiratory disease with or without complicating rheumatic fever. The tests were made with extracts of streptococcal cells containing "c" carbohydrate and nucleoprotein but not those known to contain the "x" antigen. These observations confirm the results of the present work in regard to the "c" carbohydrate and suggest that the nucleoproteins soluble at neutrality or in alkali also are not involved in the causation of streptococcal hypersensitivity.

The information obtained during this investigation does not justify further conjecture in regard to the pathogenesis of the non-suppurative complications of the post-streptococcic state. It is quite possible that the "x" substance described here is the substance responsible for the stimulation of Group A streptococcal hypersensitivity in human beings. Theoretical and experimental considerations permit the tentative exclusion of several streptococcal products from a rôle in these hypersensitivity reactions.

Many protein and at least one carbohydrate (hyaluronic acid) fractions of the streptococcal cell, in addition to the two described in this paper, have not been fully evaluated in relationship to their rôle in the causation of hypersensitivity in man.* The use of all the substances in chemically purified form as materials for injection into human beings and in immunological investigations of the type described in this paper might conclusively indict the "x" or another substance as the sensitizing antigen responsible for the incitement of post-streptococcal disease. Further progress toward the recognition, understanding and control of late non-suppurative complications of streptococcal infection awaits this event.

SUMMARY

1. Purified C carbohydrate and a non-type-specific "x" substance present in acid extracts of Group A hemolytic streptococcal cells have been used in precipitin tests with human sera.

2. Antibodies against one or the other or both of these antigens were demonstrable in the sera of certain cases of acute streptococcal sore throat at the onset of infection.

3. An anti-c antibody response occurred in 6 per cent of the patients, and an anti-x antibody response occurred in 22 per cent of the men infected by Group A hemolytic streptococci.

4. The presence or development of neither antibody could be correlated with any

*The author believes that investigation of this problem in animals other than man and, possibly other anthropoids, will be disappointing because hypersensitivity states are strikingly different among various mammalian species.

aspect of the acute suppurative phase of the illness.

5. Poststreptococcal arthritis and pneumonitis occurred more frequently in infected men in whom anti-x antibody was demonstrable in the initial serum or during convalescence than in those in whom it was not present. A similar relationship was not discovered for anti-c precipitin.

6. Anti-x antibody was infrequently discovered during the course of streptococcal respiratory disease complicated by late fever.

7. It is suggested that the "x" substance may be the antigen responsible for serious streptococcal hypersensitivity.

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Auricular Electrogram in Parasternal Leads*

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The clinical information which the electrocardiogram is able to furnish regarding the size and function of the auricles has been largely limited to studies of the standard limb leads. However, the composite picture of auricular activity as represented in these leads fails to yield the specific information which might be secured from direct leads. Leads from parasternal interspaces have been found of value in recording the variations in potential from the right auricle. Intrinsic deflections, characteristic of direct leads from the auricular surface, can be obtained from these semi-direct leads and satisfactorily correlated with clinical and roentgenological findings. Their interpretation is in accord with the experimental work of Sir Thomas Lewis and of Frank Wilson and his co-workers.

Special precordial leads have frequently been used to increase the amplitude of auricular waves in flutter, fibrillation and in tachycardias of indeterminate origin. Lewis[14] observed maximal oscillations when the electrode was placed over the right auricle in cases of fibrillation, and pointed out that enlargement of this chamber was a factor in obtaining augmented waves. Evans[8] and Szekely[18] failed to recognize any close relationship between the size of the auricular waves in fibrillation and the degree of right auricular enlargement. Drury and Iliescu,[6] using sternal and antero-posterior leads, found that coarse auricular deflections were obtained when the exploring electrode was placed to the right of the sternum. Lian and Pinchenzon[16] placed electrodes over the manubrium and paired these with leads from the right fifth interspace. Similarly, Schoenewald[17] obtained clear, upright P waves in leads from the third right interspace to the right arm. Szekely,[18] following the suggestion of Faulkner[9] and Williams and Ellis,[19] was able to determine the origin of obscure tachycardias by leads from the third right interspace, paired alternately with the right arm and the left leg; Barker, Wilson, Johnston, and Wishart[2] took leads from the upper sternum to the ensiform to demonstrate certain types of auricular tachycardia.

We have recently reported two cases of tricuspid insufficiency[7] in which large, sharply diphasic auricular waves with intrinsic deflections were found in parasternal leads, using the left leg position for the indifferent electrode. Similar conspicuous diphasic P waves in leads from the right precordium have been described by Gertz[10] and by Burton and Mehlman.[5] In both instances, however, an extracardiac factor produced a displacement of the heart, bringing the right auricle in close juxtaposition to the anterior chest wall.

In the cases studied at Toledo Hospital there has been found a close relationship between the degree of right auricular enlargement and the size and character of the auricular complexes in parasternal leads. Not only does the size of these waves conform to clinical findings of hypertrophy and dilatation, but the variations in form yield information as to the location and extent of the anterior wall of the right auricle. A large number of observations have been made on normal hearts and on those show-

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ing demonstrable right auricular strain. The taking of three leads from each parasternal interspace, paired successively with the right arm, the left arm and the left leg, presents a sequence in which the lead paired with the right arm gives the strongest positive auricular deflection, and that connected with the left leg gives the strongest negative auricular deflection, while the lead paired with the left arm occupies an intermediate position. (Figs. 1, 2 and 3.) This sequence has also been recorded by Hecht[11] and is dependent upon the auricular potential of the extremity used for the indifferent electrode.

When the influence of the indifferent electrode is greatly reduced by the use of the central terminal, according to Wilson's method, the auricular wave in parasternal leads assumes a diphasic (+ −) pattern whenever the exploring electrode is directly over and in close proximity to the anterior wall of the right auricle. The relative value of the positive and negative elements is significant, and, since it represents the changes in potential from that part of the auricle directly beneath the electrode, the distance from the sinoauricular node determines the character of the wave. The greater the distance from the sinoauricular node to that portion of the auricle directly beneath the electrode, the greater is the duration of the pre-intrinsic component and the higher is the upward deflection of the diphasic wave. Conversely, the closer the exploring electrode is to the point of origin of the excitatory impulse, the shorter is the pre-intrinsic phase and the sooner will the abrupt fall of the intrinsic deflection occur. This conforms to the findings of Lewis[15] and Wilson and his co-workers[20] in leads taken directly from the wall of the right auricle and to the observations of W. Hurst Brown [3,4] in his study of the esophageal lead. Unipolar parasternal leads in Figures 3 and 4 yield these diphasic auricular waves with the characteristic intrinsic deflection and show the variations in size and form which occur with changes in the location of the exploring electrode.

For clinical purposes, insofar as the auricular complex is concerned, parasternal leads paired with the left arm may be used in place of the unipolar leads and yield similar records as is well illustrated in Figures 2 and 3. This is presumably due to the balanced potentials of the auricular deflections as registered in unipolar left arm leads. The same is true of the Wolferth leads so arranged that the exploring electrode is placed in the parasternal interspaces and the indifferent electrode posteriorly in the interscapular space. Wolferth parasternal leads are illustrated in Figure 5.

To illustrate the character of these semidirect electrograms the following selected cases of right auricular strain are briefly presented, together with chest films and electrocardiograms. In all tracings the galvanometer was standardized at normal sensitivity (1 mv. = 1 cm.), and a chest electrode 2.5 cm. in diameter was used in taking the parasternal leads.

CASE REPORTS

Case 1. Bronchiectasis: T. L., a fifty-three-year-old white male, was admitted to Toledo Hospital in November, 1945. His chief complaint was a persistent cough of two years' duration with copious amounts of purulent sputum. He was known to have a moderate hypertension of long standing. There was no history of a coronary occlusion. Aside from a few musical rales there were no abnormal findings in the lungs, and the remainder of the physical examination was normal. The sputum contained numerous polymorphonuclear leukocytes, two per cent of which were eosinophiles. No acid-fast bacilli were discovered. The blood picture and urinalysis were within normal limits.

Films of the chest (Fig. 1) show moderate cardiac enlargement and emphysema of the

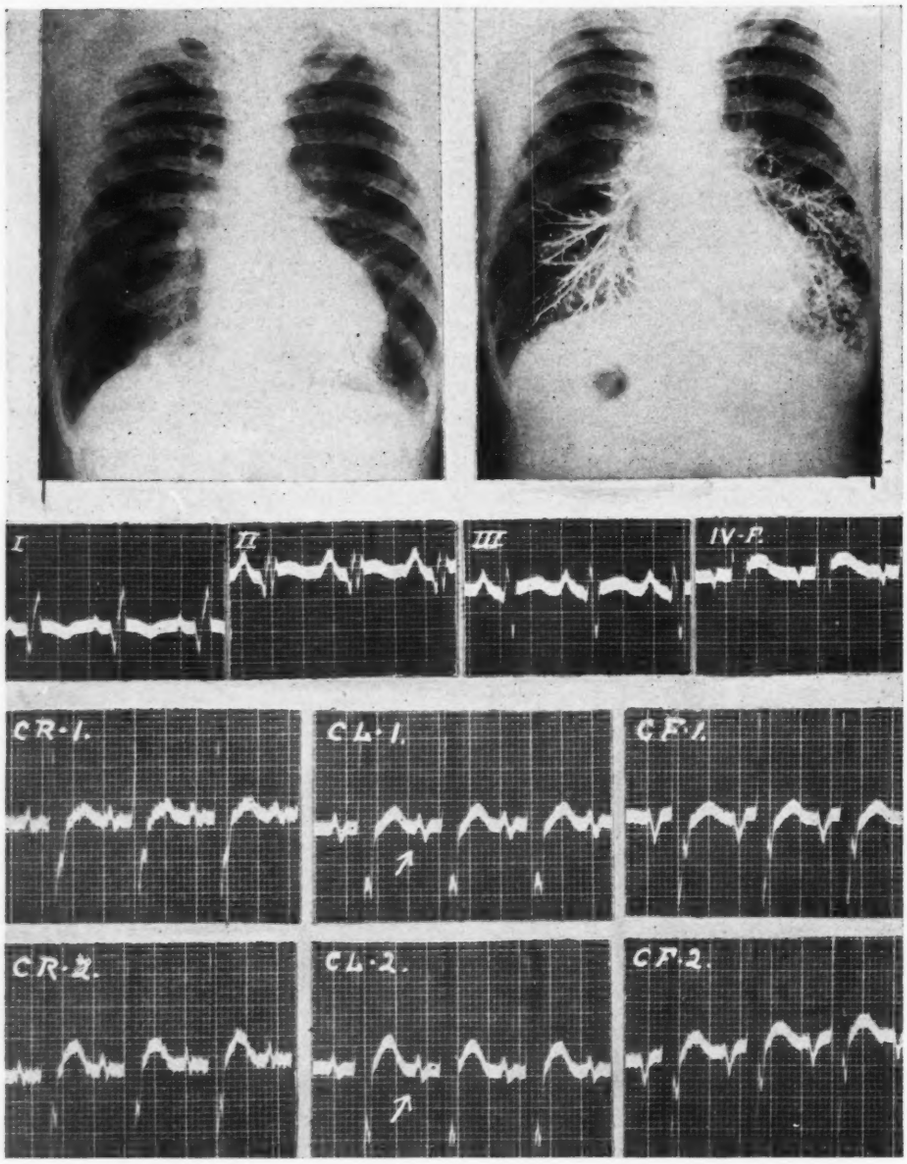

FIG. 1. Case I, chest film shows emphysema of the right base and left ventricular hypertrophy. Bronchogram shows bronchiectasis, mainly of the left lower lobe. Standard leads show large P waves in leads II and III and double R waves in II and IV-F. The negative effect of the left leg electrode and the positive effect of the right arm electrode on parasternal P waves is illustrated. Intrinsic auricular deflections occur in the fourth interspace to the left as well as to the right of the sternum.

right base. The increase in convexity of the left cardiac contour is evidence of left ventricular hypertrophy. A bronchogram shows sacular bronchiectasis chiefly of the lower left lobe.

The standard leads of the electrocardiogram are bizarre, and although the first lead is suggestive of an anterior infarction, the character of the QRS complex in the limb and precordial leads is evidence of an intraventricular conduction defect of the left bundle branch type. Auricle hypertrophy of the cor pulmonale pattern[13] is indicated by broad, high P waves in leads II and III. The parasternal leads show the sequence previously described, the P waves being most positive in CR-1 and CR-2, most negative in CF-1 and CF-2 and approximately equiphasic in CL-1 and CL-2. The finding of characteristic diphasic auricular waves in CL-1

and CL-2 with abrupt intrinsic deflections from both sides of the sternum indicates considerable enlargement of the right auricle and its proximity to the anterior chest wall beneath the fourth right and left interspaces.

CASE II. Pulmonary infarct: Dr. W. D., a dentist, 63 years of age, was admitted to Toledo Hospital in November, 1945. Until two months previously he had enjoyed excellent health. During the last two months he had become increasingly short of breath, and several days prior to admission he noted a productive cough with blood-tinged sputum and chest pains on deep breathing.

Physical examination showed a temperature of 101°F a pulse of 120, respirations 40 and a blood pressure of 150/105. Dullness and increased vocal fremitus were found in the right base posteriorly. Râles were present in both apices and scattered throughout the left side. The heart was moderately enlarged. There were no murmurs. The liver was palpable 2 cm. below the costal margin. There was no edema, and the examination was otherwise normal. The leukocyte count on admission was 12,000 with 86 per cent polymorphonuclears. There was no anemia. The urine contained a trace of albumin, and the blood nonprotein nitrogen was slightly elevated. Blood cultures were negative. There were a few gram-positive cocci in the sputum which were not pneumococci. The clinical diagnosis was pneumonia of the right lower lobe and cardiac hypertrophy with moderate decompensation.

The patient's course in the hospital was stormy. Although the pneumonic process cleared under penicillin therapy, his cough and dyspnea continued. He was digitalized with some improvement. Two episodes of intense pain were interpreted as splenic and pulmonary infarctions.

The chest film reproduced (Fig. 2) was taken after resolution of the pneumonia and the absorption of a small amount of pleural fluid seen in previous films. The heart shows enlargement in all diameters and extends some distance to the right of the sternum. The aortic shadow is broad and heavy. There is a single infarct in the right middle lobe. The chest is otherwise clear.

Electrocardiograms show left axis deviation in the standard leads, large P waves, prolonged auriculo-ventricular conduction time (0.22 sec.) and evidence of diffuse myocardial damage. Parasternal leads from the fourth interspace when connected with a left arm electrode and with a unipolar central terminal, show the characteristic diphasic wave with the sharp intrinsic deflection of a semidirect auricular electrogram. A smaller diphasic wave is seen in a lead from the left of the sternum. It is evident that the right auricle is in close apposition to the anterior chest wall at these points. This may have been the result of the stress placed on the right side of the heart by acute pulmonary disease, or it may have resulted from the general cardiac hypertrophy producing a forward displacement of an already enlarged auricle. Electrocardiograms including parasternal leads taken in June, 1946, six months after the records shown in Figure 2, show much smaller, less abrupt parasternal P waves and support the former interpretation.

CASE III. Rheumatic endocarditis: R. McK., seven years of age, was admitted to Toledo Hospital in January, 1946. Infancy and childhood had been normal until the age of four when he developed Sydenham's chorea, and a heart murmur was discovered. Upon recovery his tonsils and adenoids were removed. A second attack of chorea occurred at the age of six. He was kept in a convalescent home for twelve months and given prophylactic sulsonamide therapy. Two weeks prior to admission his nervous symptoms recurred for the third time. There had been no arthritic manifestations.

Examination revealed a mildly febrile white boy with a slight speech defect and occasional twitching of the shoulders, arms and hands. The throat was injected. The chest was normal. The pulse was regular but rapid. The heart was not appreciably enlarged. There was a blowing systolic murmur, grade 3, audible over the entire precordium, but loudest at the apex. A soft mid-diastolic murmur was present which was accentuated in the left lateral position. The clinical impression was recurrent Sydenham's chorea with rheumatic carditis and involvement of the mitral valve.

Chest films show a moderate cardiac enlarge-

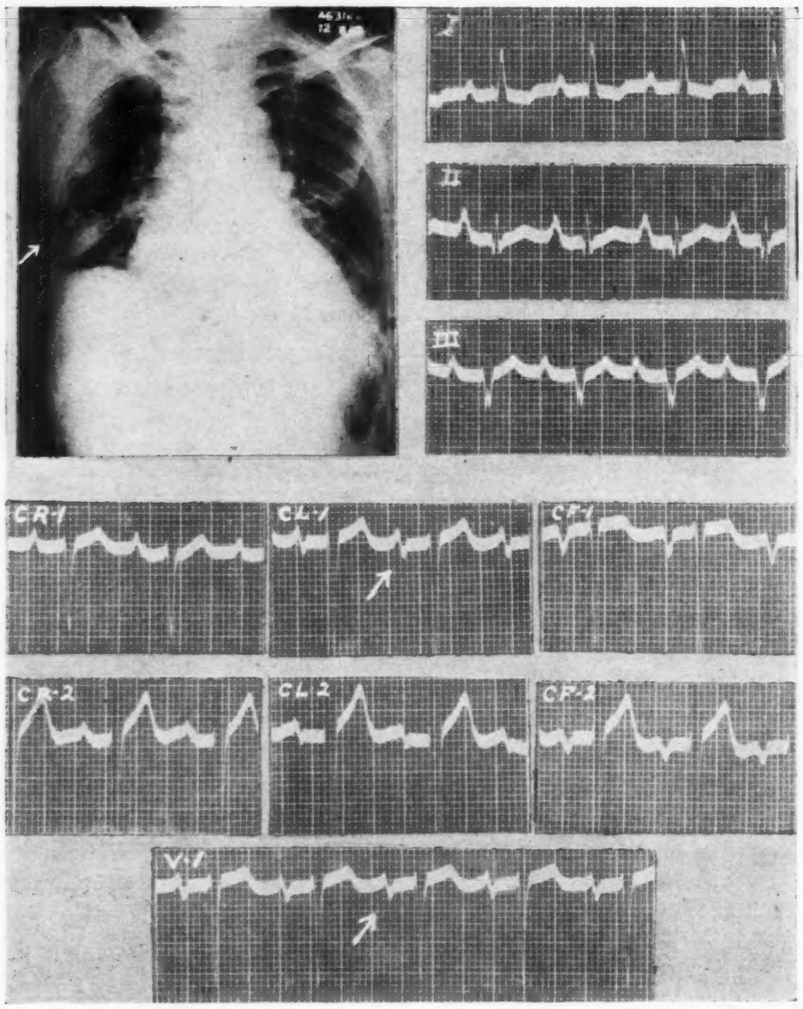

FIG. 2. Case II, chest film shows general cardiac hypertrophy with widening of the aortic shadow and the residual changes following a pulmonary infarct. Standard leads show left axis deviation, evidence of myocardial damage, prolonged P-R interval and large auricular waves in lead II. Intrinsic auricular deflections are conspicuous in CL–1 and unipolar lead V-1. A smaller diphasic P wave is present in CL–2.

ment with some fullness in the pulmonary conus but no other abnormality. The limb leads of the electrocardiogram show a right axis deviation and a prolonged auriculoventricular conduction time (0.24 sec.). There are large P waves in leads I and II which conform to the mitral pattern of auricular hypertrophy. Four leads were taken from each parasternal interspace by changing the site of the indifferent electrode and by using Wilson's central terminal. (Fig. 3.) The similarity between unipolar parasternal auricular complexes and those obtained by using the left arm as the site of the indifferent electrode is illustrated. The pull toward positivity when the right arm is coupled with the parasternal leads, and the negative effect of the left leg electrode on the parasternal auricular deflection is also shown.

Diphasic waves from the right auricle with abrupt intrinsic deflections were obtained from the third and fourth interspaces, both to the right and to the left of the sternum. These are clearly seen in CL-4th R (CL-1), V-4th R (V-1), CF-4th L (CF-2), CL-3rd L, and V-3rd L. From the character of these auricular waves and the positions from which they were obtained,

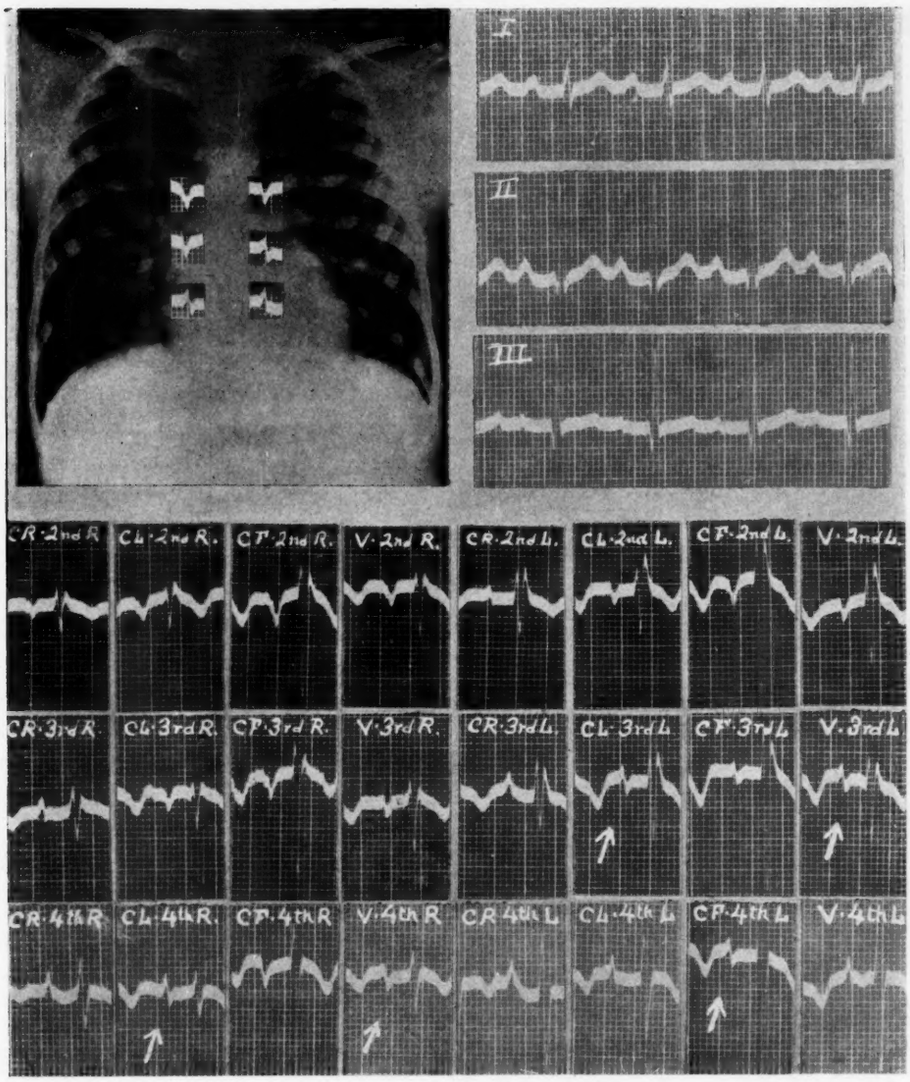

FIG. 3. Case III, chest film shows a moderate diffuse cardiac hypertrophy. Inserts are unipolar auricular electrograms taken from the positions indicated. Standard leads show large P wave in leads I and II. P-R measures 0.24 seconds. Moderate right axis deviation. Parasternal leads are taken from the second, third and fourth interspaces, right and left of sternum and paired with electrodes at the three extremities with a central terminal. Lettering is self-explanatory. Diphasic auricular waves with intrinsic deflections are seen in CL third left, unipolar third left, CL fourth right, unipolar fourth right and in CF third and fourth left.

it is proper to infer that the right auricle has undergone considerable enlargement, and that it lies close to the anterior chest wall to the left as well as to the right of the sternum.

CASE IV. Rheumatic carditis: D. F., a girl twelve years of age, had been a patient in Toledo Hospital during November and December, 1945, at which time she had an acute rheumatic pancarditis with involvement of the aortic and mitral valves, relative tricuspid insufficiency and cardiac decompensation. Under rest and digitalis medication she had progressed favorably and was greatly improved when examined in March, 1946. The heart was much smaller, the signs of tricuspid insufficiency had disappeared, the liver was no longer palpable, and there was no peripheral edema. There was still present a mitral systolic murmur of moderate

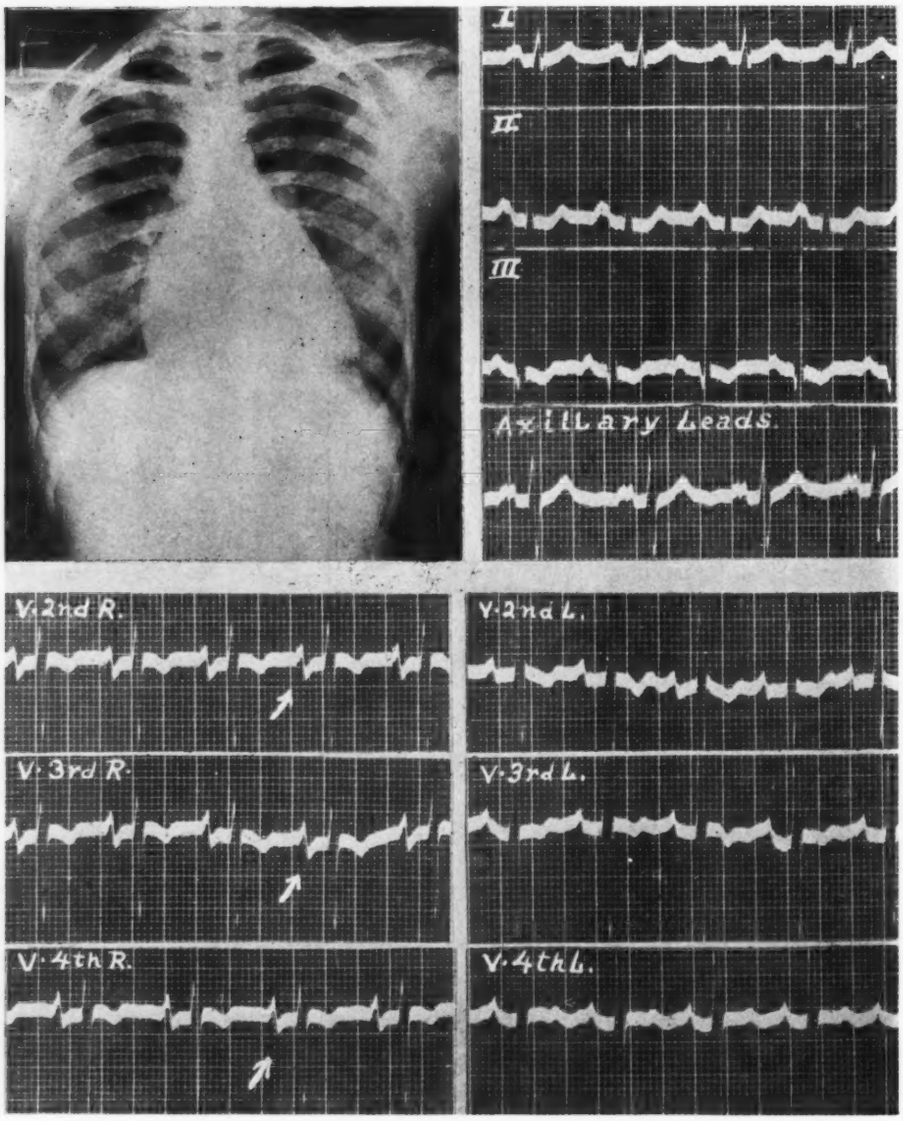

FIG. 4. Case IV, chest film shows a uniformly enlarged heart with a rounded pulmonary conus. The aortic knob is absent. Electrocardiogram shows right axis deviation, large P waves in leads I and II and broad, notched auricular waves in Whitten's axillary lead. The parasternal leads show diphasic auricular electrograms with intrinsic deflections in unipolar derivations from the interspaces to the right of the sternum.

intensity, but no diastolic murmur or presystolic thrill could be discovered.

The chest film (Fig. 4) shows a uniformly enlarged heart with considerable prominence of the pulmonary conus and a full rounded contour of the right cardiac border. The aortic knob is absent. The lung fields are clear. The electrocardiogram still shows a right axis deviation, but this is not as marked as in previous records. Conduction time, formerly increased, is now normal. P waves are broad and notched; this deformity of the auricular complex is well illustrated in a Whitten lead taken from right and left axillary spaces. In this lead the P wave measures 0.12 sec. in duration and shows a definite bifurcation which may represent a block of Bachmann's interauricular bundle.[1]

Unipolar parasternal leads were taken from the second, third, and fourth interspaces to the right and left of the sternum. Large diphasic

auricular waves are found in all the right parasternal leads. They show the sharp fall of the intrinsic deflection characteristic of semidirect auricular electrograms and represent the position and size of the right auricle. It is interesting to note that the pre-intrinsic phase of the auricular complex becomes higher and sharper as the exploring electrode is moved downward on the chest. The downstroke of the intrinsic deflection occurs earlier at the higher levels where the exploring electrode is closer to the sino-auricular node. In electrograms taken during the height of the previous attack of rheumatic carditis, diphasic waves were also obtained in leads from the left of the sternum. The absence of such waves in this record clearly indicates a reduction in the size of the auricle and conforms to the clinical improvement and the absence of the signs of tricuspid regurgitation.

CASE V. Congenital heart: L. S., a bookkeeper twenty-six years of age, had been cyanotic since birth. There was no history of physical defects in the family. He escaped the usual diseases of childhood and had not suffered from respiratory infections. Deformities of the hands and feet were first noticed at the age of twelve. He has never been able to engage in work or recreation which required physical exertion because of a prohibitive shortness of breath.

He was examined in February, 1946, at which time he presented the classical symptoms of congenital heart disease of the Fallot type, with general cyanosis, dyspnoea on slight exertion, marked clubbing of fingers and toes and with soft tissue deformities about the ankles and wrists. There were no clinical signs of pulmonary complications. The heart was moderately enlarged and on palpation a double systolic impulse could be felt over the lower precordium. Auscultation revealed a loud systolic murmur, maximum in the fourth left interspace which was transmitted more clearly to the right than to the left. In the second left interspace a high pitched systolic murmur could be heard, but this was not accompanied by a thrill. The brachial pressure was 124/86 and the systolic pressure was 140 in the lower extremity by palpation.

Blood counts showed a compensatory polycythemia with an erythrocyte count of 7,260,000 and a hemoglobin of over 140 per cent. The leukocyte count was 6,500 with a normal differential. *X*-rays of the extremities showed a broadening of the distal portion of the long bones, periosteal thickening and subperiosteal proliferation, especially noticeable in the lower third of the tibia and fibula. Roentgenograms of the chest showed the heart to have a modified coeur-en-sabot configuration with no fullness of the pulmonary conus. The right ventricle was conspicuous in the lateral film. Fluoroscopy showed an enlarged and somewhat displaced aorta and a synchronous pulsation in the aorta and in the right auricle. The diagnosis was tetralogy of Fallot with secondary hypertrophic osteoarthropathy.

Standard electrocardiograms showed a normal rhythm and right axis deviation. The auricular waves were tall and broad in leads I and II. Parasternal leads were taken from the second, third, and fourth right and left interspaces and were paired with an indifferent central terminal and also with the indifferent electrode in the interscapular area. Leads from the right interspace showed large diphasic P waves with an abrupt intrinsic deflection, characteristic of semidirect auricular electrograms. In this patient the diphasic waves appeared at a higher level than in other cases and this suggests an altered position of the heart as related to the location of the exploring electrodes. (Fig. 5.) The presence of these typical auricular electrograms indicates an enlargement of the right auricle and its displacement by the hypertrophied right ventricle.

The patient was operated by Dr. A. Blalock of Baltimore in May and an anastomosis established between the right common carotid and the right pulmonary arteries. Marked improvement followed this surgical procedure. Cyanosis almost disappeared, and the dyspnoea was greatly relieved. The blood count fell to 6,000,000 and the hemoglobin to 120 per cent. On June 20th electrocardiograms taken from the right parasternal spaces failed to show the characteristic diphasic waves which had been previously observed (Fig. 5). The change was taken to indicate a diminished strain on the

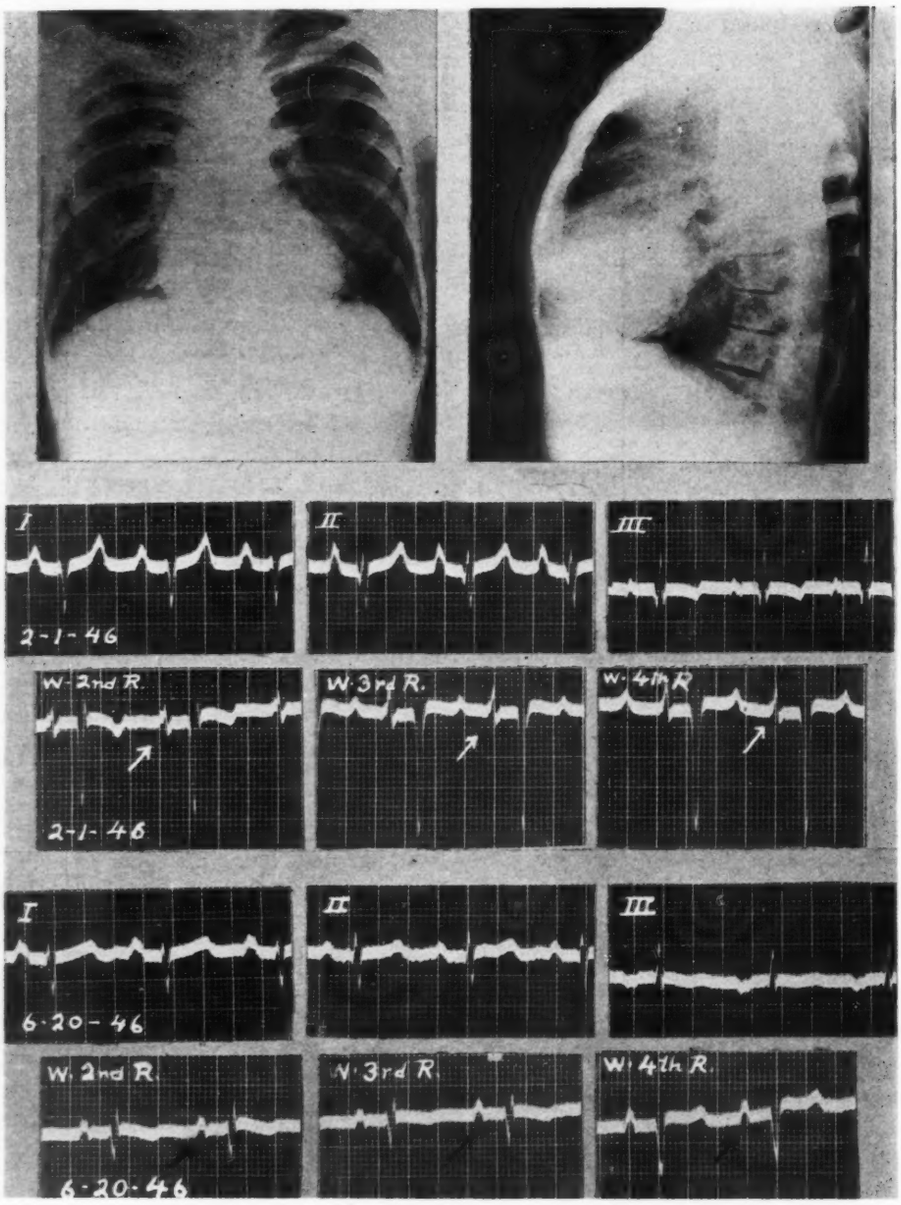

FIG. 5. Case V, frontal and lateral chest films in the tetralogy of Fallot, showing a modified coeur-en-sabot configuration with no convexity in the region of the pulmonary conus. Retrocardiac space is clear. The right ventricle presses against the anterior chest wall. The electrocardiogram shows a right axis deviation and large P waves in leads I and II. Parasternal leads paired with an electrode in the interscapular space show diphasic auricular waves with intrinsic deflections (white arrows). The lower electrocardiograms, taken seven weeks after a Blalock operation, show changes in the size and form of the T waves of standard leads. In the parasternal leads from the second, third and fourth right interspaces the auricular waves are now of the conventional type (black arrows) and no longer show the intrinsic deflection of the direct electrogram.

right auricle and a reduction in its size. Fluoroscopic examinations and oblique films confirmed this observation.

COMMENTS

In connection with our study of these semidirect leads it has been observed that in decompensation with right auricular enlargement diphasic waves were obtained from both right and left interspaces. As compensation was restored these waves were found only in leads from the right of the sternum.

It was also noted that when there was hypertrophy of both ventricles the right auricle was displaced to the right and downward, whereas when right ventricular hypertrophy was dominant the right auricle was displaced to the right or to the right and upward, as in Case v. When the right auricle itself was greatly enlarged intrinsic deflections were found in the auricular waves from the left as well as from the right interspaces.

When the character of the auricular complex returns to the conventional type and the intrinsic deflection can no longer be recorded in semidirect parasternal leads, it is evidence that the wall of the right auricle has receded to a degree which prevents the exploring electrode from receiving the potential variations of a semidirect electrogram. In Case II the diphasic waves disappeared from the parasternal leads within six months. In Case IV the intrinsic deflections disappeared from the left side of the sternum and at the time of the last observation could only be found in the right parasternal leads. In Case V, the tetralogy of Fallot, parasternal leads taken seven weeks after the carotid pulmonary artery anastomosis was established failed to reveal the diphasic auricular waves previously recorded. The change is illustrated in the electrocardiograms of Figure 5. Such observations on these and on other cases where clinical improvement has occurred furnish convincing evidence that the finding of these diphasic auricular waves with the abrupt intrinsic deflection when present in parasternal leads, has a definite clinical significance and indicates an excessive strain on the right auricle.

SUMMARY

Parasternal leads using equipment ordinarily available yield satisfactory semidirect electrograms from the right auricle when it is under excessive strain. The use of a central terminal for the indifferent electrode was found to be more satisfactory than either the left leg or the right arm, as these locations exert a strong influence on the directional character of parasternal auricular deflections. Parasternal leads paired with electrodes on the left arm, in the interscapular space, or with a central terminal may be used interchangeably without altering the characteristic auricular deflections under discussion. By the presence and location of intrinsic auricular deflections information can be gained regarding the degree of enlargement and the position of the right auricle. Five selected cases showing the correlation of auricular electrograms with clinical and roentgenological findings are presented.

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Investigations of the Cerebrospinal Fluid in Cases of Rheumatoid Arthritis*

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THE symptomatology of rheumatoid arthritis includes a large number of neurological symptoms which indicate that both the central and autonomic nervous systems are involved in this disease. This circumstance is particularly striking when the disease has a rapidly progressive course. In such cases a whole series of more or less pronounced neurological symptoms may be met with. For instance, pareses in the muscles of the extremities may be present which lead to difficulties in performing various movements. These pareses are especially striking either in the flexor muscles of the fingers, with the result that the hand can be only incompletely clenched actively or cannot be clenched at all; or in the extensor muscles of the fingers, with the result that the hand is in a clawlike position and the fingers cannot be straightened fully. In the early stage of the disease the fingers can be both flexed and straightened to the full extent passively, which shows that the obstacle to movement is not localized in the joints. Not until a later stage, when true joint symptoms have developed, is an arthogenous mechanical obstacle to the performance of movements added. In association with the pareses, rapidly increasing muscular atrophy of the muscles of the extremities sets in (often to considerable degree before local joint symptoms have developed), accompanied by hydrops and thickening of the capsules and therefore not the result only of inactivity. Along with these pareses, a pronounced coarse-waved tremor of an irregular type is met with in the fingers in these cases. Trophic disturbances in the form of local hyperhidrosis of the hand and feet, pigment changes in the skin on the dorsal surface of the hands and fingers, nail changes, atrophy of the skin and decalcification of the juxta-articular ends of the bones, which are so often encountered in more severe cases of arthritis, indicate that the vegetative nervous system has also been affected or is still involved.

As has been indicated, all the neurological symptoms mentioned may be present in severe, rapidly progressive cases of rheumatoid arthritis. Sometimes, however, one symptom or several symptoms predominate, while others are less pronounced or are absent altogether. In many, especially in the milder cases of chronic polyarthritis, neurological symptoms are not very prominent; but by careful examination, even in these cases, one or several of the symptoms indicated above can often be recognized.

In cases of rheumatoid arthritis in which clinical signs of involvement of both the central and autonomic nervous systems are found, it might reasonably be expected that indications of an affection of the central nervous system would also be detectable in the cerebrospinal fluid. No previous in-

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† The head of the State Race Biological Institute, Professor Gunnar Dahlberg, L.L.D. assisted with the statistical work-up.

vestigations in this direction appear to have been made. In isolated cases increased protein values have been found in the spinal fluid in cases of rheumatoid arthritis. Thus, employing Mestrezat's diaphanometric method, Graber-Duvernay in 1939 found an increased protein content of the spinal fluid in eight of fifteen cases of rheumatoid arthritis. The method employed is now considered so unreliable that probably no positive conclusions can be drawn from Graber-Duvernay's investigations. In 1942, Sundelin published thirty-four cases of rheumatoid arthritis in which the spinal fluid had been examined by the Izikowitz method. In thirteen of the cases (38 per cent), clearly pathological protein values were obtained, in that the total protein was significantly elevated in five cases, the globulin content in six cases, the albumin content in three cases and the globulin-albumin quotient raised in eight cases and lowered in one case. Ludwig, Short and Bauer, 1943, examined cerebrospinal fluids from, *inter alia*, fifty-nine cases of rheumatoid arthritis and found increased protein values in four cases (6.8 per cent) and pathological colloidal gold curves in five cases (8.5 per cent). The analytical method employed by the authors was Denis-Ayer's nephelometric procedure which, according to Izikowitz (1941), is reliable on the whole but is impaired by chance deviations of considerable magnitude (standard deviation = 10.50 ± 0.74 mg. per cent).

A clinically serviceable and sufficiently exact method of determining both the total protein and the albumin and globulin fractions in the spinal fluid was described by Izikowitz in 1941. The normal values for the protein content and its various fractions found by Izikowitz were re-investigated by Wiberg (1943), Rune Olsson (1944) and Eeg-Olofson (1944), the results showing good agreement with the Izikowitz values. As to the method, reference should be made to Izikowitz's work.

Since 1940, I have examined the spinal fluid in 141 cases of rheumatoid arthritis: thirty-eight men and one hundred and three women. The cases in question were not selected in any way, except insofar as only clinically certain cases of rheumatoid arthritis were included. Three of the male cases also exhibited ankylopoietic spondylarthritis. With regard to the degree of severity of the disease in these patients, seventeen may be classified as mild, fifty-five as moderately severe and sixty-nine as severe cases. The duration of the disease before examination varied between four months and twenty years. By far the greater number of cases, however, had been affected between one and one-half and three years. When the examination was made, all the cases but two were afebrile. The two febrile cases had temperatures of 38°C.

The specimens were taken by lumbar puncture between L_4 and L_5 with the patient in a recumbent position. About 12 cc. was drawn off and this amount of fluid was immediately divided up into different portions for examination of the cell content, qualitative protein investigation according to Nonne-Apelt and Pandy, colloidal gold-sol reaction, Meinicke's II reaction and quantitative determination of the total protein, albumin and globulin by the Izikowitz method. The quantitative protein determinations were made by Dr. Izikowitz in his laboratory. This investigator was unaware of the clinical diagnosis of the cases from which the spinal fluids had been taken. In addition to chronic rheumatoid arthritis cases, parallel cases of chronic neurological diseases and prolapse of the nucleus pulposus were subjected to similar examination of the fluid with no diagnosis indicated.

The investigations of the spinal fluids

were made before any treatment of the patients had been initiated. In sixty-three cases the patients had previously received gold treatment, as a rule several months or years earlier. In twelve of these cases gold treatment had been discontinued as recently as two to four months before the investigation. In all the cases Meinicke's II reaction was negative.

Of the 141 cases investigated, 58 (41 per cent) exhibited protein values pathological in one way or another, and some of these cases also showed pathological gold-sol curves. (Table IA, IB.) In seven cases with normal protein values the gold-sol reaction was pathological. In six of the cases with raised protein values the cell content of the fluid was increased (4 or more cells per mm.^{3}) at the same time. In only one case with a pathological cell increase (7.5 leukocytes and 5.5 lymphocytes per mm^3.) were all the protein values normal. Thus a total of 66 cases (46.8 per cent) exhibited spinal fluids which were pathologically changed in one way or another.

TABLE IA

CASES OF RHEUMATOID ARTHRITIS WITH INCREASED PROTEIN CONCENTRATION OR GLOBULIN-ALBUMIN QUOTIENT IN THE SPINAL FLUID (MALE PATIENTS)

Case No.	Age	Total Protein in Mg. per 100 Cc.	Globulin in Mg. per 100 Cc.	Albumin in Mg. per 100 Cc.	Globulin-Albumin Quotient	Cells per 3.2 Mm.^{3}	Gold-sol Reaction
3	38	62.97	*14.21*	48.76	0.29	4.16	
5	45	57.63	*21.04*	36.59	*0.57*	*60.80*	
6	50	25.50	7.90	17.60	*0.45*	1.92	
12	31	30.01	10.64	19.37	*0.55*	2.88	0011100000
14	25	37.65	13.23	24.42	*0.54*	1.92	*0123311000*
17	33	28.57	7.65	20.92	*0.37*	3.84	0122100000
19	53	36.45	*14.20*	22.25	*0.64*	*47.04*	0000000000
24	35	30.16	9.71	20.45	*0.47*	0.96	1111111110
28	49	29.27	7.77	21.50	*0.36*	10.56	
29	57	27.86	8.73	19.13	*0.46*	2.88	1222111000
30	23	39.06	*15.69*	23.37	*0.67*	5.44	1110000000
31	53	53.98	*20.37*	33.61	*0.61*	0	1111111110
32	46	53.05	10.71	42.34	0.25	*41.60*	
34	28	24.92	6.62	18.30	*0.36*	2.88	*1233335333*
35	45	18.69	6.50	12.19	*0.53*	0	1111000000
36	15	35.00	9.98	25.02	*0.40*	0	0111111000

Of the fifty-eight cases with pathological protein values, fifteen were men and forty-three women.

TABLE IB

CASES OF RHEUMATOID ARTHRITIS WITH INCREASED PROTEIN CONCENTRATION OR GLOBULIN-ALBUMIN QUOTIENT IN THE SPINAL FLUID (FEMALE PATIENTS)

Case No.	Age	Total Protein in Mg. per 100 Cc.	Globulin in Mg. per 100 Cc.	Albumin in Mg. per 100 Cc.	Globulin-Albumin Quotient	Cells per 3.2 Mm.^{3}	Gold-sol Reaction
41	19	20.07	5.38	19.69	*0.37*	5.12	
49	11	21.70	6.94	14.76	*0.47*	0	
51	36	*51.42*	10.29	*41.13*	0.25	1.92	*0044330000*
52	46	*63.45*	*27.63*	35.82	*0.77*	*12.80*	*0116666200*
53	38	20.27	5.35	14.92	*0.36*	4.48	
56	15	*65.08*	*21.95*	*43.13*	*0.51*	3.20	
57	31	30.28	8.62	21.66	*0.40*	3.20	0011110000
59	43	27.94	9.58	18.36	*0.52*	4.80	1111111000
60	38	45.17	*11.93*	33.24	*0.36*	*16.00*	
69	22	47.62	8.69	*38.93*	0.22	2.88	0012221000
71	38	*67.23*	*21.04*	*46.19*	*0.46*	*22.40*	1122221000
72	22	*56.16*	*12.51*	*43.65*	0.29	9.28	*1112321110*
74	37	39.95	*11.86*	28.09	*0.42*	0.96	*1332110000*
75	35	24.28	8.67	15.61	*0.56*	0	0000000000
77	52	26.53	7.84	18.69	*0.42*	2.88	1111122111
81	23	26.32	7.14	19.18	*0.37*	2.88	0111100000
86	33	45.32	*13.31*	32.01	*0.42*	0.96	0111100000
87	40	32.66	9.73	22.93	*0.42*	0	1122221100
89	33	23.34	7.94	15.40	*0.52*	3.20	1111111000
93	38	*50.89*	*11.98*	*38.91*	0.31	3.20	1122111000
97	54	32.28	9.37	22.91	*0.41*	*12.80*	0111100000
99	50	35.37	*19.28*	16.09	*1.20*	0	0122110000
102	23	60.27	5.06	11.21	*0.45*	1.92	
103	40	27.44	8.32	19.12	*0.44*	0.96	1111110000
104	46	27.42	8.83	18.59	*0.47*	1.92	2221111100
105	41	31.09	8.46	22.63	*0.37*	2.88	
106	40	26.91	8.03	18.88	*0.43*	0	
107	34	21.63	6.33	14.90	*0.42*	2.88	1111100000
109	46	39.76	11.15	28.61	*0.39*	1.92	
111	28	41.56	*20.50*	21.06	*0.97*	0.96	1111100000
112	38	27.74	9.09	18.65	*0.49*	1.92	1111100000
113	54	23.96	6.62	17.34	*0.38*	1.92	*1224444444*
114	18	24.00	6.41	17.59	*0.36*	3.84	1111110000
116	19	20.34	5.64	14.70	*0.38*	0.96	1111111000
117	28	19.71	5.79	13.92	*0.42*	0.96	1111000000
119	37	27.74	7.71	20.03	*0.38*	1.92	0000000000
121	53	42.41	*12.29*	30.12	*0.41*	1.92	1111111111
126	53	43.93	*11.44*	32.49	0.35	2.88	1111110000
127	17	21.64	7.04	14.60	*0.48*	7.04	1111100000
133	19	19.90	7.69	12.21	*0.63*	0.96	*1122222232*
138	53	28.50	7.50	21.00	*0.36*	0.96	1111100000
140	29	18.21	6.30	11.91	*0.53*	1.92	1121110000
141	17	27.73	8.21	19.52	*0.42*	0.96	1221100000

The total protein was above normal limits in six cases, all women, the values varying between 51 and 67 mg. per cent. According to Izikowitz, the mean value for the total protein of the spinal fluid in normal women is 31 mg. per cent and the maximum "permissible" statistically calculated normal value is 48.7 mg. per cent.

The globulin content exceeded normal limits in seventeen cases, five of which were men and twelve were women. The values for the men varied between 14 and 21 mg. per cent, as against a mean value of 7.7 mg.

per cent and a maximum "permissible" value of 13.7 mg. per cent for normal males. The values for the women were between 11 and 28 mg. per cent, as against the mean value of 6 mg. per cent and the maximum "permissible" value of 10.7 mg. per cent in normal females.

The albumin content was increased in six cases, all women, and varied between 38.91 mg. per cent and 46.19 mg. per cent; as against the mean value of 22.9 mg. per cent and the maximum "permissible" value of 38.39 mg. per cent in normal persons.

The globulin-albumin quotient proved to be abnormally high in fifty-two cases, fourteen of which were men and thirty-eight women. In the men the elevated quotient was between 0.36 and 0.67, as against a mean value of 0.24 and a maximum "permissible" value of 0.34 in normal males. In the women the elevated quotient was between 0.36 and 1.20, as against a mean value in normal females of 0.25 and a maximum "permissible" value of 0.36.

Of the three patients who had ankylopoietic spondylarthritis simultaneously with rheumatoid arthritis, two had completely normal protein values in the spinal fluid, while the third had a raised globulin-albumin quotient of 0.36.

A summary of the various combinations of pathologically increased protein values is given in Table II.

A statistical study of the material with regard to total protein, the different protein fractions and the globulin-albumin quotient showed (Table III), *inter alia*, no significant difference between the values found for men and women. In respect to the total protein value, however, a larger material would probably show that the total protein is higher in men than in women, i.e., in agreement with the findings in healthy persons. No difference between the sexes could be established with regard to the globulin-albumin quotient; which would imply that both globulin and albumin values are higher in men than in women. Thus, to sum up, it could be established that in these arthritic cases there was approximately the same difference between the sexes with respect to total protein, globulin and albumin values as is found in normal subjects.

TABLE II
PATHOLOGICALLY INCREASED PROTEIN VALUES IN THE SPINAL FLUID

Increase in	Men	Women
Quotient only	10	29
Globulin only	1	1
Albumin only	..	1
Globulin, quotient	4	6
Total protein, albumin	..	1
Total protein, globulin, albumin	..	2
Total protein, globulin, quotient	..	1
Total protein, globulin, albumin, quotient	..	2
Total	15	43

If a comparison is made between the protein values obtained and the normal values found in a large series by Izikowitz, no considerable difference appears in the total protein values. On the other hand, it is certain that in cases of rheumatoid arthritis the globulin value is increased, the albumin value lowered and the quotient considerably elevated. The mean value for the globulin-albumin value found here is 0.36 as compared with 0.25 normally.

Since the globulin content of the spinal fluid proved to be elevated in cases of rheumatoid arthritis, it was of interest to investigate the colloidal gold reaction. Kabat, Landow and Moore (1942) showed that in a number of diseases the colloidal gold reaction was conditioned entirely by gamma globulin and not by the albumin fraction, but it was pointed out at the same time that the gamma globulin, which in these cases affects the gold-sol reaction, must in some way be different from that

TABLE III

PROTEIN VALUES (MG PER CENT) AND GLOBULIN/ALBUMIN QUOTIENT IN THE SPINAL FLUID IN CASES OF RHEUMATOID ARTHRITIS

	Men			Women			Difference D ± Σ(D)
	No.	M ± Σ(M)	σ	No.	M ± Σ(M)	σ	
Total protein	38	36.3 ± 1.8	11.0	103	30.9 ± 1.0	10.1	5.4 ± 2.0
Globulin	38	9.3 ± 0.6	3.9	103	8.0 ± 0.4	3.9	1.3 ± 0.7
Albumin	38	27.0 ± 1.4	8.5	103	22.9 ± 0.7	7.5	4.1 ± 1.6
Globulin-albumin quotient	38	0.36 ± 0.021	0.13	103	0.36 ± 0.014	0.14	0.0 ± 0.025

normally found in the spinal fluid, since normal spinal fluid does not give a pathological gold curve.

In this material the gold-sol reaction was investigated in 107 cases, twenty-seven of which were men and eighty women.* In fifteen cases, three men and twelve women, i.e., in 14 per cent of the cases investigated, the gold-sol reaction gave a positive (pathological) result. In eight cases, thus in somewhat more than half, the pathological gold-sol reaction was obtained in cases that had protein values which were abnormal in one way or another. In the other seven cases the protein reaction in the spinal fluid was within normal limits. Closer scrutiny of the cases which had abnormal gold-sol reactions and at the same time elevated protein values reveals (Table I) that all but one had an absolute or relative increase in the globulin content of the spinal fluid. But as the gold-sol reaction was normal in 76 per cent of the patients who had increased spinal fluid protein values, and furthermore was positive in a number of cases with normal protein values, it is manifest that the positive reaction in some cases could not be conditioned only by a quantitative increase in globulin values. Thus it is clear that in rheumatoid arthritis there must exist some other, hitherto unknown, factor which in certain cases results in a pathological gold-sol curve.

It is now of interest to determine whether the degree of severity of rheumatoid arthritis had any connection with the pathologically increased protein values in the spinal fluid. The grouping of our material in respect to severity of disease must naturally be somewhat schematic. Consideration was paid to the general course of the disease: whether it exhibited a rapid progression; whether multiple, few, or single joints were involved; and whether the joint symptoms were severe or slight. On this basis the material was divided into three groups: mild, moderately severe and severe cases. The number of cases falling into each group has already been stated and this is also shown in Tables IVA and IVB.

From Table IVA it is evident that, on the whole, the protein and quotient values are

TABLE IVA

PROTEIN VALUES IN THE SPINAL FLUID IN VARYING DEGREES OF SEVERITY OF THE ARTHRITIC DISEASE PROCESS

Degree of Severity	No. of Cases	Total Protein	Globulin	Albumin	Quotient
Men					
I	8	36.8	8.5	28.3	0.32
II	14	32.7 ± 2.8	8.3 ± 1.0	24.3 ± 2.1	0.35 ± 0.030
III	16	39.2 ± 3.0	10.6 ± 1.1	28.6 ± 2.4	0.38 ± 0.038
Women					
I	9	34.6	8.0	26.6	0.31
II	41	31.3 ± 1.7	7.8 ± 0.6	23.5 ± 1.3	0.34 ± 0.020
III	53	29.9 ± 1.3	8.1 ± 0.6	21.8 ± 0.8	0.38 ± 0.022

* The gold-sol reaction was not carried out in all the cases because of a shortage of the necessary reagent during certain periods of the war years.

TABLE IVB
DISTRIBUTION OF SPINAL FLUID PROTEIN VALUES ACCORDING TO THE DEGREE OF SEVERITY OF THE ARTHRITIC DISEASE

Protein Value		Degree of Severity			
		I	II	III	Total
Men					
Pathological value	No.	2	5	8	15
	%	13.3	33.3	53.4	100.0
Normal value	No.	6	9	8	23
	%	26.1	39.1	34.8	100.0
Women					
Pathological value	No.	5	16	22	43
	%	11.6	37.2	51.2	100.0
Normal value	No.	4	25	31	60
	%	6.7	41.7	51.6	100.0
Both sexes					
Pathological value	No.	7	21	30	58
	%	12.1	36.2	51.7	100.0
Normal value	No.	10	34	39	83
	%	12.0	41.0	47.0	100.0

similar in the three groups and that the degree of severity of the disease does not appear to affect the protein values. If the cases with pathological and normal protein values are considered according to the degree of severity of the disease process (Table IVB) it is found that the distribution is the same irrespective of whether or not the cases exhibit abnormal spinal fluid values.

The degree of severity of the disease is also reflected by the erythrocyte sedimentation rate (S.R.). If the sedimentation rate in the different cases (Table V) is scrutinized, it is found that no considerable differences can be established between cases with pathological and those with normal protein contents of the cerebrospinal fluid.

Another factor which may conceivably affect the protein content of the cerebrospinal fluid is the duration of illness. The material has therefore been divided up into cases dating back at most one year and cases with a duration of more than one year. (Table VIA.) The analysis shows that duration of illness does not appear to have

TABLE V
THE ERYTHROCYTE SEDIMENTATION RATE IN PATIENTS WITH PATHOLOGICAL AND NORMAL PROTEIN VALUES IN THE SPINAL FLUID

Spinal Fluid Protein Value	No. of Cases	Mm./One Hr.	Mm./Two Hr.
Men			
Pathological	15	55 ± 8	89 ± 7
Normal	23	42 ± 6	72 ± 7
Women			
Pathological	43	57 ± 5	83 ± 5
Normal	60	51 ± 4	80 ± 4

any connection with the protein content of the cerebrospinal fluid. On the other hand, if the duration of illness in cases with abnormally elevated spinal fluid protein values and in those with normal protein values is considered (Table VIB), it is found that, in general, cases with pathological protein values appear to be of shorter duration.

As a number of the arthritic cases investigated had previously received gold treatment for months or even years, and as this might conceivably have affected the protein in the spinal fluid, this circumstance has received special attention. It appears, however, that no significant difference in values was obtained in patients who were treated and those who were not treated with gold. (Table VII.)

As has been mentioned previously, Nonne-Apelt's and Pandy's protein reactions were carried out parallel with the quantitative protein determinations. Izikowitz (1941), later Gripwall (1943) and Wiberg (1943) have shown that there is a considerable discrepancy between the results of the Nonne-Apelt and the Pandy reactions, and the concentrations of total protein and globulin in the spinal fluid. In the present arthritis series, too, very unsatisfactory agreement was found between the quantitative total protein values obtained and the qualitative protein reactions (Table VIII). Of the cases with pathological values in the spinal fluid (both sexes) only 7 per cent

TABLE VIA

SPINAL FLUID PROTEIN VALUES IN VARYING DURATION OF ILLNESS IN ARTHRITIS

Duration of Illness	No. of Cases	Total Protein	Globulin	Albumin	Quotient
Men					
Less than 1 year	18	39.6 ± 2.7	10.4 ± 0.8	29.2 ± 2.2	0.37 ± 0.031
More than 1 year	19	33.6 ± 2.3	8.4 ± 0.9	25.2 ± 1.7	0.34 ± 0.030
Women					
Less than 1 year	26	28.4 ± 1.6	6.9 ± 0.4	21.5 ± 1.4	0.34 ± 0.015
More than 1 year	77	31.7 ± 1.2	8.3 ± 0.5	23.4 ± 0.9	0.36 ± 0.018

exhibit a positive Nonne and 11 per cent a positive Pandy reaction. Even if doubtful reactions are added, not more than 27 per cent of positive Nonne and 34 per cent of positive Pandy reactions are included. Furthermore, it is evident that among the cases with protein values within normal limits, there is as large a percentage of positive or doubtful Nonne and Pandy reactions as there is among cases with pathological spinal fluid protein levels.

If the protein values for the seven cases which exhibited positive cell findings in the spinal fluid are examined (Table IXA), it is found that in one case all the protein values were normal; in one case the quotient was abnormally high; in three cases the globulin and quotient were elevated; in one case the total protein, globulin and

TABLE VIB

AVERAGE DURATION OF ILLNESS IN PERSONS WITH RHEUMATOID ARTHRITIS GROUPED ACCORDING TO PATHOLOGICAL OR NORMAL PROTEIN VALUES IN THE SPINAL FLUID

Protein Value	No. of Cases	Duration of Illness (Years)	
		Average	Median
Men			
Pathological	14	1.0 ± 0.16	1
Normal	23	3.3 ± 0.78	2
Women			
Pathological	43	3.5 ± 0.50	2
Normal	60	4.2 ± 0.54	3
Both sexes			
Pathological	57	2.9 ± 0.4	1.5
Normal	83	3.9 ± 0.4	3

TABLE VIII

THE NONNE-APELT AND PANDY PROTEIN REACTIONS IN PATIENTS WITH PATHOLOGICAL AND NORMAL PROTEIN CONTENTS OF THE SPINAL FLUID

Protein Value		Positive	Doubtful	Negative	Total
Nonne					
Men					
Pathological	No.	2	6	6	14
	%	14.2	42.9	42.9	100.0
Normal	No.	2	9	12	23
	%	8.7	39.1	52.2	100.0
Women					
Pathological	No.	2	5	35	42
	%	4.8	11.9	83.3	100.0
Normal	No.	1	13	45	59
	%	1.7	22.0	76.3	100.0
Both sexes					
Pathological	No.	4	11	41	56
	%	7.1	19.6	73.2	100.0
Normal	No.	3	22	57	82
	%	3.7	26.8	69.5	100.0
Pandy					
Men					
Pathological	No.	2	5	7	14
	%	14.2	35.8	50.0	100.0
Normal	No.	3	8	11	22
	%	13.6	36.4	50.0	100.0
Women					
Pathological	No.	4	8	30	42
	%	9.5	19.0	71.5	100.0
Normal	No.	1	17	41	59
	%	1.7	28.8	69.5	100.0
Both sexes					
Pathological	No.	6	13	37	56
	%	10.7	23.2	66.1	100.0
Normal	No.	4	25	52	81
	%	4.9	30.8	64.3	100.0

TABLE VII

SPINAL FLUID PROTEIN VALUES IN CASES OF ARTHRITIS TREATED OR NOT TREATED WITH GOLD

Group	No. of Cases	Total Protein	Globulin	Albumin	Globulin-Albumin Quotient
Men					
Treated with gold	15	34.0 ± 2.8	8.9 ± 1.1	25.1 ± 2.1	0.36 ± 0.033
Not treated with gold	23	37.8 ± 2.3	9.6 ± 0.5	28.2 ± 1.8	0.36 ± 0.028
Women					
Treated with gold	48	30.9 ± 1.4	8.0 ± 0.5	22.9 ± 1.0	0.36 ± 0.023
Not treated with gold	55	30.8 ± 1.4	7.9 ± 0.6	22.9 ± 1.0	0.35 ± 0.017

quotient were pathologically increased and in one case the total protein, globulin, albumin and quotient were all abnormally high.

TABLE IXA

SPINAL FLUID PROTEIN VALUES IN PATIENTS WITH INCREASED NUMBER OF CELLS IN THE SPINAL FLUID

Case Number	Cells per 3.2 Mm.³	Total Protein in Mg. per 100 Cc.	Globulin in Mg. per 100 Cc.	Albumin in Mg. per 100 Cc.	Globulin-Albumin Quotient
32 ♂	41.6	53.05	10.71	42.34	0.25
97 ♀	12.8	32.28	9.37	22.91	*0.41*
19 ♂	47.04	36.45	*14.20*	22.25	*0.64*
5 ♂	60.8	57.63	*21.04*	36.59	*0.57*
60 ♀	16.0	45.17	*11.93*	33.24	*0.36*
52 ♀	12.8	*63.45*	*27.63*	35.82	*0.77*
71 ♀	22.4	*67.23*	*21.04*	*46.19*	*0.46*

If the whole material is scrutinized with respect to protein content and cell findings in the spinal fluid (Table IXB) the frequency of increased cell counts seems to be somewhat greater in cases with increased protein contents. The material is not sufficiently large, however, to afford definite data in this respect.

Finally, an inquiry was also made as to whether the patients with rheumatoid arthritis who exhibited pathologically raised protein values in the spinal fluid had any clinically overt neurological symptoms. It was found, first, (Table X) that some cases exhibited a pronounced tremor of the fingers and hands of a peculiar type, which can best be characterized as a combination of a relatively short-wave tremor (which is both visible and palpable) and a more irregular athetotic coarse-wave tremor. A tremor of this kind was observed in about half the cases with increased protein values in the spinal fluid.

TABLE IXB

DISTRIBUTION OF INCREASED CELL COUNTS IN THE SPINAL FLUID OF PATIENTS WITH ELEVATED AND NORMAL SPINAL FLUID PROTEIN VALUES

Protein Value	No. of Cases	No. of Cases With At Least 4 Cells (Leukocytes and Lymphocytes) in the Spinal Fluid Count		
		No.		
Pathological	58	6	10.3 ± 4.0	Diff. 9.1 ± 4.17
Normal	83	1	1.2 ± 1.2	

TABLE X

NEUROLOGICAL SYMPTOMS IN FIFTY-EIGHT CASES OF RHEUMATID ARTHRITIS WITH INCREASED PROTEIN VALUES IN THE SPINAL FLUID

Symptom	Men	Women	Total
Tremor	10	18	28
Paresis	13	38	51
Muscular atrophy	12	35	47
Vegetative disturbances	12	19	31
Miscellaneous	2	7	9

Another symptom frequently met with was an appreciable paretic impairment of function of the hands and fingers. This showed itself in an incapacity either to clench the fists entirely, or, if that could be

done, in a markedly weakened hand clasp. Obviously, local changes in the joints, in the form of swelling of the joint capsules, hydrops and pain, may impede or prevent the clenching of the hand, but such cases have not been regarded as paretic. Only in those patients who exhibited reduced power of movement in the hands with joint symptoms of subordinate importance was paresis of the flexors of the fingers (or in some cases the extensors of the fingers) considered to be present. Such pareses of the fingers were present in fifty-two of the fifty-eight cases with abnormally elevated spinal fluid protein.

Visible atrophy of the interosseous muscles was also met with in a large number of cases, specifically in forty-seven of the fifty-eight with pathological spinal fluids.

Vegetative disturbances in the form of abnormal sweating, marked cyanosis or edematous swelling of the skin of the hands, pigment changes in the skin and nail changes (including one patient with skin changes resembling scleroderma in the fingers) were encountered in thirty-one cases of the fifty-eight in this series.

General muscular atrophy or muscular atrophy localized to single large joints was observed in nine cases.

As regards neurological manifestations in cases of rheumatoid arthritis, it may be said by way of summary that all except one of the cases with a pathologically increased protein content in the spinal fluid exhibited one or more neurological symptoms. An analysis of the number of such symptoms gives the following figures:

No neurological symptoms.....	1 woman
One neurological symptom.....	2 men and 4 women
Two neurological symptoms....	2 men and 11 women
Three neurological symptoms...	2 men and 19 women
Four neurological symptoms....	9 men and 8 women

The above mentioned neurological symptoms were also met with in about the same proportions in the cases of rheumatoid arthritis with normal protein values in the spinal fluid at the time of the examination.

SUMMARY

The spinal fluid was examined in 141 cases of rheumatoid arthritis, thirty-eight men and 103 women, of whom fifty-eight (41 per cent) exhibited a protein content that was pathological in one way or other, fifteen (14 per cent) gave a pathological gold-sol reaction and seven showed an increased spinal fluid cell count. Altogether sixty-six cases (46.8 per cent) were found to have spinal fluids which were pathologically altered in some way.

Statistical examination of the results shows, *inter alia*, that in cases of rheumatoid arthritis the average spinal fluid globulin value is increased and the average spinal fluid albumin value lowered, resulting in a raised average globulin-albumin quotient. Further, it was shown that the abnormal increases in spinal fluid protein values are not dependent on the degree of severity of the arthritic disease process and are little affected by the duration of the disease.

The frequency of increased cell counts in the spinal fluid appears to be somewhat greater in cases with elevated protein contents.

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Sulfadiazine Sensitivity with Demonstrable Skin-sensitizing Antibody in the Serum*

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SINCE Prausnitz and Küstner in 1921[1] described the phenomenon of passive transfer and established the skin-sensitizing antibody as the basis of a large group of allergic reactions, the possibility of demonstrating such antibodies in cases of idiosyncrasy to drugs of simple chemical structure has interested both clinicians as a diagnostic method and immunologists as evidence of the chemical nature of antigens. In 1926, Biberstein[2] reported passive transfer of sensitivities to mercury salts, salvarsan, bismuth and pyramidon, and a few other similar reports have appeared in foreign literature.[3] However, numerous attempts by researchers in this country to reproduce these same results have failed and for years the existence of transferable antibodies for drugs of simple structure was doubted by most authorities in this country,[4,5] although Kern[6] in 1938 did describe a case of rhinitis and bronchial asthma due to phthalic anhydride (a simple, nitrogen-free compound), with an immediate urticarial reaction to scratch test and a typical passive transfer reaction to this substance. More recently, Feinberg and Watrous[7] reported similar cases of asthma and rhinitis in workers exposed to halazone and chloramine T, both simple synthetic drugs, also showing typical urticarial reactions by direct scratch tests and on passive transfers.

Soon after the introduction of the sulfonamide drugs, numerous cases of acquired sensitivity to these compounds were reported. The usual story was that the patient tolerated the first course of the drug without symptoms, or, if the first course was prolonged, developed fever or a skin rash or both, only after receiving the drug for seven to ten days. However, when the drug was administered a second time weeks or months later, the skin rash or fever appeared within a few hours after the first dose.[8] In many instances, the existence and specificity of the sensitivity were proven clinically by intentionally repeating small doses of the causative and related drugs,[9-14] but attempts to confirm the diagnosis by skin tests were usually unsuccessful. In a few patients with drug rashes positive patch tests were obtained[15,16,17] but scratch and intracutaneous tests with the drugs were uniformly negative.[13,18–23] Leftwich[23] reported positive reactions when the sensitive patients were tested intracutaneously with serums of persons who were taking the causative drugs, but other authors had negative results with similar drugs[22] as well as with normal human serum to which the drugs had been added.[24] In a few instances, skin tests were made with diazotized sulfonamides coupled to normal human serum, but the results were again negative.[9,25]

Likewise, attempts to demonstrate antibodies in the serums of sulfonamide-sensitive patients by precipitin tests[9,18] and by passive sensitization of guinea pigs gave negative results.[9,18] Passive transfer of sul-

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fathiazole sensitivity to normal human skin was reported by Shaffer, Lentz and McGuire[26] in cases of contact dermatitis due to topical use of the drug but similar tests with serums of other patients sensitive to sulfathiazole[13] and other sulfonamides[18,27] failed.

Recently, the authors have had the opportunity to study the serum of a patient who had an unusually severe reaction to sulfadiazine, and this serum showed the presence of a demonstrable skin-sensitizing antibody to that drug.

The patient, a twenty-four year old woman, was admitted to the Roosevelt Hospital, January 5, 1946, because of general erythema, vomiting, bloody diarrhea and collapse. There was no past history of allergic disease or drug reactions, but her mother had had hay fever. Six months before admission, the patient had taken sulfadiazine for several days for an upper respiratory infection, with no untoward reaction.

On the day before admission, she noticed a mild adenitis of the cervical lymph nodes, and was advised by a physician to take sulfadiazine. She took the first dose of 1.0 Gm. before dinner, and forty minutes later became acutely ill with a feeling of fullness in her head, severe itching and redness of the skin, followed by severe vomiting and diarrhea, with blood in the vomitus and stools. Within six hours, she was in a state of collapse with a rapid, thready pulse. During this same time, a single large bleb, approximately 5 cm. in diameter, appeared on her left buttock. Her leukocyte count was 20,000. The acute symptoms abated the next day and she made an uneventful recovery.

Intracutaneous tests with various foods were normal. A patch test with sulfadiazine powder showed a negative reaction, but when a patch test with 10 per cent sodium sulfadiazine was applied to the unbroken skin, the area began to itch within four minutes. When this patch was removed ninety minutes later, there was a definite wheal with erythema at the site. Because of the acuity of the patient's symptoms and the fact that a wheal reaction was obtained by application of the soluble salt of sulfadiazine to the unbroken skin, no scratch or intracutaneous test was attempted but blood for passive transfer was taken on the fifteenth day.

Passive transfer, carried out with the usual technic, showed a marked reaction to 1 per cent sodium sulfadiazine, with a wheal 1.5 cm. in diameter, while the control test on non-sensitized skin gave no reaction. Other sites tested with timothy and ragweed pollens, dog epithelium, feathers and house dust showed no reaction. The positive reaction to 1 per cent sodium sulfadiazine was demonstrated in skin sites sensitized with the same serum in six different normal test subjects, producing wheals 1.4 to 2.0 cm. in diameter in all cases. Testing with 0.1 per cent sodium sulfadiazine gave a smaller but definite reaction. When the serum was heated four hours at 56°C., it no longer gave a definite transfer reaction to 1 per cent sodium sulfadiazine.

TABLE 1
PASSIVE TRANSFER REACTIONS OF DILUTIONS OF WA. SERUM WITH SULFONAMIDE DRUGS

Sites Made with Wa. Serum	Reaction On Test After 48 Hours With			
	Sodium Sulfadiazine 1%	Sodium Sulfapyridine 1%	Sodium Sulfathiazole 1%	Sulfanilamide Saturated Solution
Concentrated	++++	++++	++++	0
1–10	++++	+++	+++	0
1–100	+++	++	++	0
1–1000	++	+	++	0
1–10,000	±	0	0	0
Control	0	0	0	0

In another experiment, quadruplicate sites were sensitized with 0.1 ml. of serum and with dilutions of the serum 1–10, 1–100, 1–1000 and 1–10,000 in saline. One series of sites was tested with 1 per cent sodium sulfadiazine, another with 1 per cent sodium sulfapyridine, the third with 1 per cent sodium sulfathiazole, and the fourth with a saturated solution of sulfanilamide, which contains slightly less than 1 per cent. As shown in Table 1, the first three drugs gave definite reactions in sites made with the 1–1000 dilution; sodium sulfadiazine gave a questionable reaction with the 1–10,000 dilution

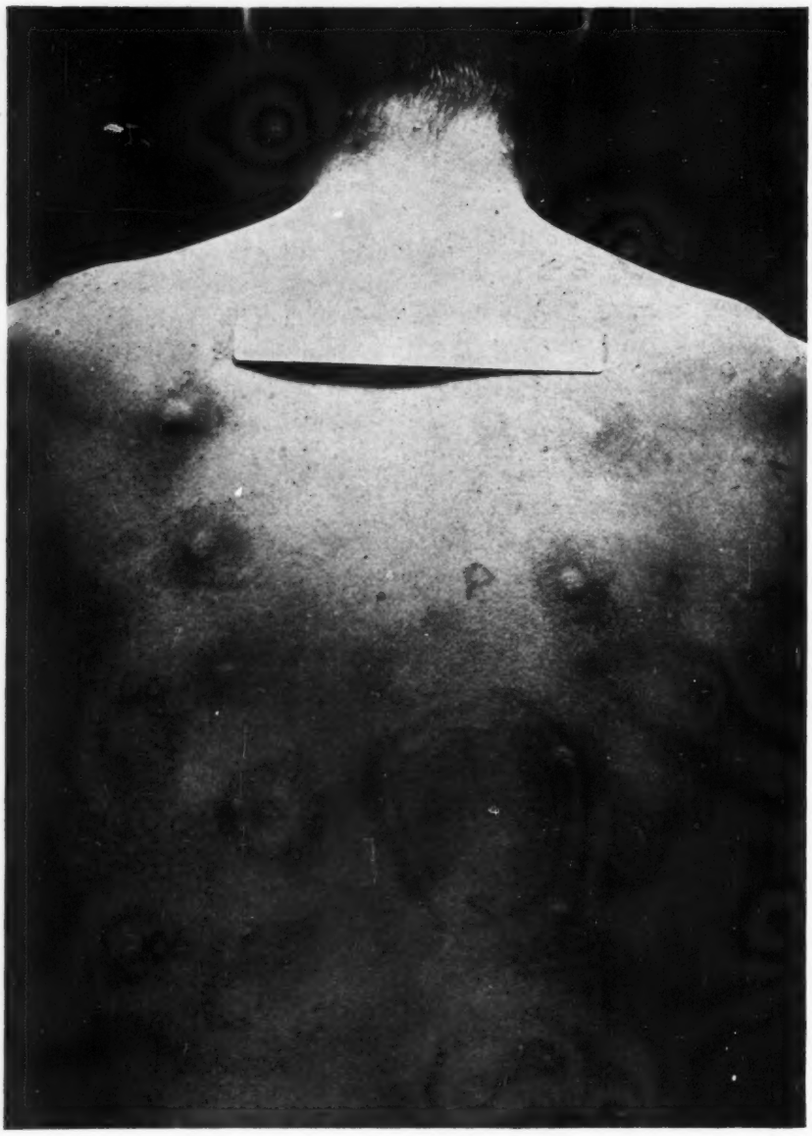

FIG. 1. Reactions obtained on passive transfer. On left, sites made with Wa. serum, concentrated, 1–10, 1–100, 1–1000 and 1–10,000 respectively, tested with 1 per cent sodium sulfadiazine. On right, sites made with Wa. serum (undiluted) tested with 1 per cent sodium sulfadiazine, 1 per cent sodium sulfapyridine, 1 per cent sodium sulfathiazole, and saturated solution of sulfanilamide. Control tests on non-sensitized skin at extreme right.

of the serum, while sulfanilamide gave no reaction. The failure of sulfanilamide to react was not due to its slightly lower concentration, since in another experiment a similar serum site had been shown to react definitely with 0.1 per cent sodium sulfadiazine.

Figure 1 illustrates the results of a similar but less complete test in which serial dilutions of serum were tested with 1 per cent sodium sulfadiazine, but only sites of the undiluted serum were tested with the other drugs.

For a neutralization experiment, the sensitive serum was mixed with equal volumes of solutions of sodium sulfadiazine of various strengths (0.1 per cent, 1 per cent and 10 per

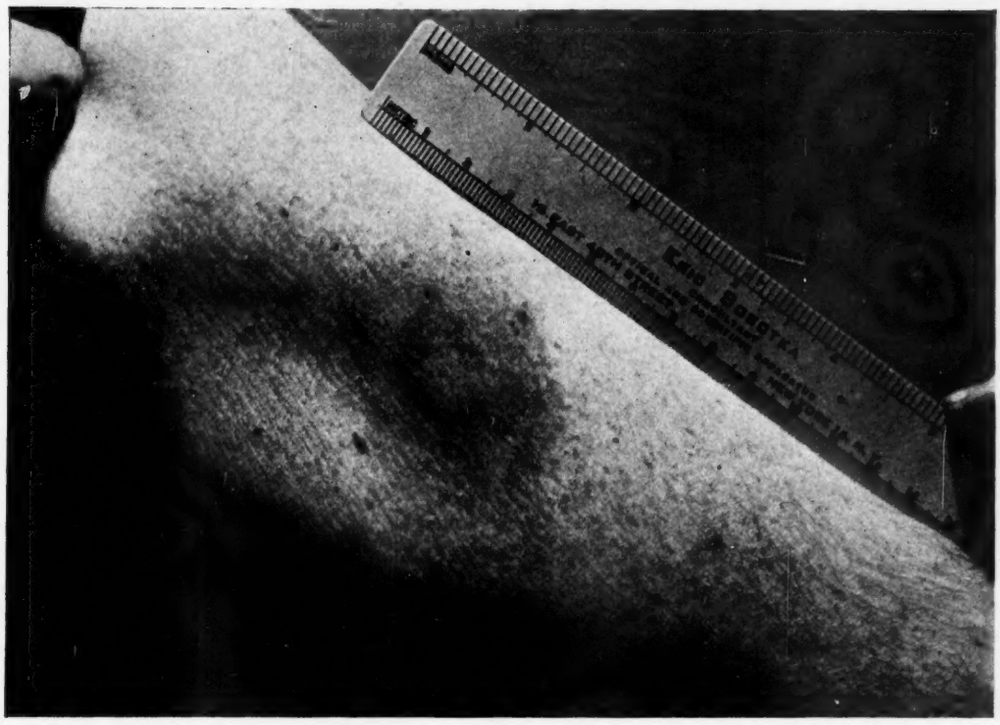

FIG. 2. Reaction produced in sensitized site by ingestion of 1.0 Gm. of sulfadiazine.

cent respectively); with serum from a patient receiving sulfadiazine; and as a control, with saline. When sites in normal skin were sensitized with these mixtures and tested forty-eight hours later with 1 per cent sodium sulfadiazine, all reacted approximately equally, showing no evidence of neutralization of the skin-sensitizing antibody. The same sites were tested a second time, twenty-four hours later, with 1 per cent sodium sulfadiazine, and again showed strong reactions, indicating that the antibody had not been neutralized or exhausted by the first testing.

In other experiments, a sensitized site was not tested intracutaneously, but the test subject ingested 1.0 Gm. of sulfadiazine. In four such tests a strong reaction with a wheal 2 to 3 cm. in diameter, and a surrounding red erythema 6 to 7 cm. in diameter appeared in forty to ninety minutes. (Fig. 2.) Ingestion of 2.0 Gm. of sulfanilamide or 1.0 Gm. of sulfapyridine gave no reaction. Ingestion of 1.0 Gm. of sulfathiazole gave rise to an area of redness and itching, 3 by 5 cm., at the sensitized site, appearing two and a half hours later and lasting two hours without wheal formation. The day after the ingestion of these other drugs, the site was tested by ingestion of sulfadiazine and reacted strongly. When sulfadiazine was ingested a second time, after two days, there was no reaction, indicating that the antibody was exhausted or neutralized by this method of testing.

Precipitin tests with the sensitive serum and various dilutions of sodium sulfadiazine were negative. An attempt to sensitize the skin of a guinea pig by the intracutaneous injection of 0.1 ml. of the serum gave negative results. Two ml. of serum were also injected intra-abdominally into a virgin female guinea pig and a Dale test performed two days later. There was no reaction with sodium sulfadiazine, although the control test with histamine gave an active contraction.

On the basis of these observations, sulfa-

diazine may be added to the simple chemical compounds which have been shown to stimulate the formation of demonstrable antibodies in the human body and to react with these antibodies in the passively sensitized skin site. Since the plasma proteins have been shown to bind sulfadiazine,[28] one may assume that such a reaction takes place to form a protein antigen. There is nothing in the observed facts to prove or disprove this hypothesis, but if the combination is assumed to take place in the sensitized site, it must occur almost instantaneously, since the urticarial reaction is just as rapid as with typical protein antigens.

The skin-sensitizing antibody in this serum resembled that of a highly sensitive hay fever patient in its activity (as measured by the dilution test), in its thermolability, in its failure to sensitize passively a guinea pig and in its failure to form a precipitate with the antigen. It differed in that the antibody was not easily neutralized by the antigen *in vivo* or *in vitro*. However, the difference may have been in the allergen rather than the antibody, the rapid diffusibility of sulfadiazine removing it from the site before the antibody was completely neutralized.

Similar studies of the serums of two other patients known to be sensitive to sulfadiazine, one of whom had a severe general reaction 20 minutes after taking 1 Gm. of the drug, showed no demonstrable skin-sensitizing antibody. These observations and the reports of other cases in the literature, suggest that the passive transfer of sensitivity to sulfadiazine is rare. It is doubtful if this method will often prove useful in diagnosis. However, the fact that it may occur is of interest and might occasionally be of practical use.

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Review

Fungus Diseases Encountered in General Hospital Practice*

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SUPERFICIAL fungus infections of skin, hair and nails are often chronic and resistant to treatment but rarely affect the general health of the patient. The deep mycoses are frequently fatal; they may be acute, subacute or chronic and present major problems in diagnosis and treatment.

ACTINOMYCOSIS

The clinical syndrome of actinomycosis may be caused by either the anaerobic *Actinomyces bovis* or the several species of aerobic *Actinomyces* now called *Nocardia*.[1] *A. bovis* may be found in the gums and tonsils[2,3,4,5] of apparently healthy normal individuals, and various types of pathogenic *Nocardia* have been isolated from the soil.[6]

Approximately 90 per cent of actinomycetic infections are of the anaerobic type.[6] The disease occurs in all parts of the world and in all races. It is most prevalent between the ages of fifteen and thirty-five and affects men twice as frequently as women.

There are four clinical forms of the disease: (1) cervicofacial, (2) pulmonary, (3) abdominal and (4) generalized. The diagnosis should be suspected from the clinical picture, but must be confirmed by the demonstration of the characteristic organisms in pus, sputum, biopsy specimens (Fig. 1) or by the isolation of the organism on appropriate media. *A. bovis* should be grown in veal infusion medium under anaerobic conditions. The aerobic *Nocardia* grow on blood agar or Sabouraud's medium.[7]

The prognosis is best in the cervicofacial form of the disease and becomes progressively worse in the pulmonary, abdominal and generalized infections.[8–13]

Both the aerobic and anaerobic types of actinomycosis respond slowly to treatment with either sulfonamides or penicillin.[14,15,16] A few patients have been cured by chemotherapy, but in many instances the symptoms persist or the apparently cured patient relapses after some months. Extensive and repeated surgery is required frequently, not only for drainage of abscesses but for the destruction and elimination of as much as possible of the infected tissue. Iodide therapy is of little value alone but should be used as a supplement to chemotherapy to promote resolution and absorption of granulomatous tissue. *X*-ray therapy has been used to stimulate the healing of indolent lesions.

PARA-ACTINOMYCOSIS

A number of organisms belonging to the family of Actinomycetaceae have some superficial resemblance to *Actinomyces* and produce subacute and chronic infections which must be differentiated from cases of true actinomycosis. These infections are known in the literature as (1) mycotic rat-bite fever,[17] (2) Haverhill fever,[18] (3) erysipeloid,[19,20,21] (4) Bacteroides infection,[23,24,25] (5) actinobacillosis[26,27] and (6)

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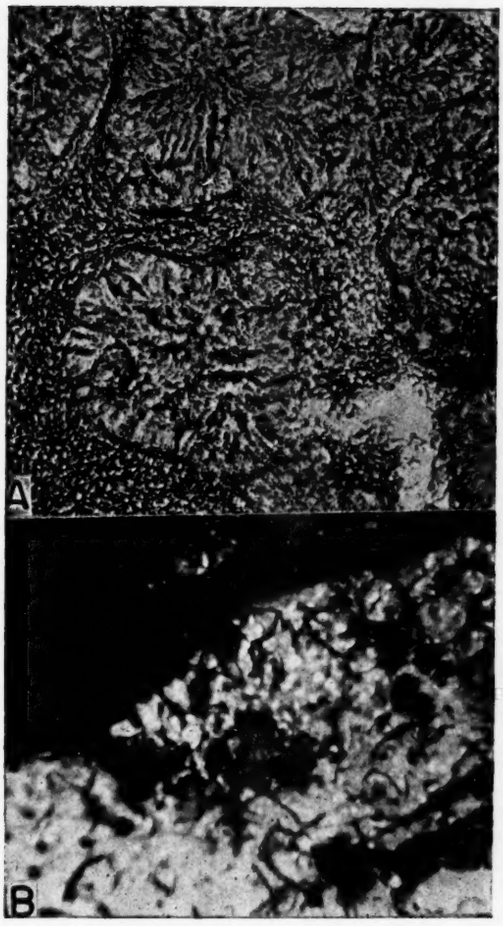

FIG. 1. *Actinomyces bovis*. A, granule in pus from draining sinus. × 162; B, crushed granule stained by Gram's method to show gram-positive branching filaments. × 1080.

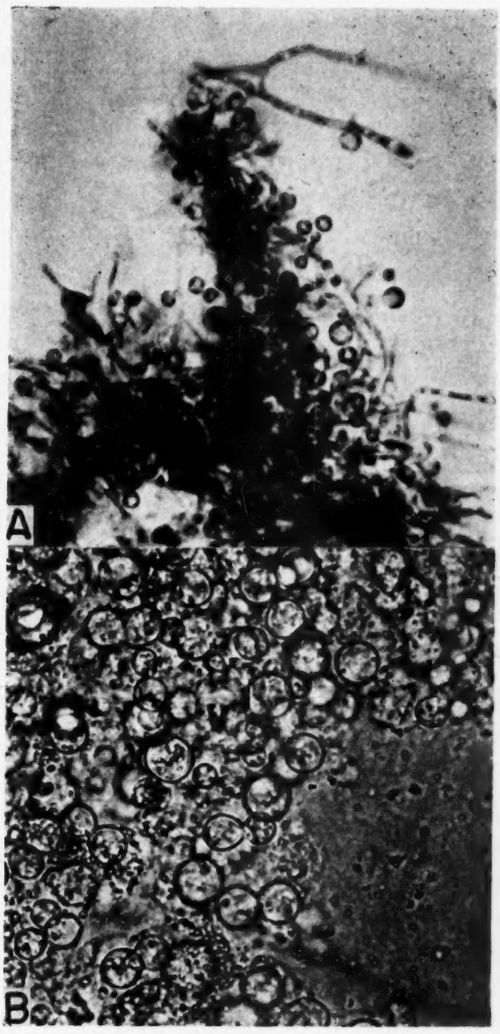

FIG. 2. *Blastomyces dermatitidis*. A, filamentous form of room temperature culture on Sabouraud's glucose agar. × 658; B, budding yeast-like form in pus from lesion. × 762.

botryomycosis or staphylococcic actinophytosis.[28] This last mentioned infection is caused by a Staphylococcus, but one that produces, for some unknown reason, chronic granulomatous lesions with draining sinuses and "granule" formation which under the low power of the microscope resembles closely the typical "sulfur granule" of *A. bovis*.

NORTH AMERICAN BLASTOMYCOSIS

Blastomycosis is caused by *Blastomyces dermatitidis*. This is an exogenous infection but its source in nature has not been discovered.[29] A few instances of the disease have been reported from England, but all the other authentic cases have occurred within the borders of the United States and Canada.[30] It occurs with greatest frequency in the Mississippi Valley and in the Southeastern states.[31] It may begin at any age between six months and eighty years, but is most often seen between the ages of twenty and forty. All races are susceptible, but males are infected nine times as frequently as females.

Two characteristic clinical forms of blastomycosis are known: (1) the cutaneous and (2) the systemic. The cutaneous form is

chronic and may persist for eight to ten years before spreading to the internal organs.[32,33] The systemic form of the disease is more acute, usually resulting in death in six months to three years.[31,34] Most of the systemic cases begin in the lungs, suggesting inhalation as the mode of infection.

The diagnosis is established by finding the characteristic double-contoured budding forms in pus, sputum and biopsy material or by culturing the organism on Sabouraud's medium. (Fig. 2.) Progressive cases usually have complement-fixing antibodies present in the serum.[35] The patients may or may not have positive skin tests of the delayed tuberculin type to autogenous or stock cultures of *B. dermatitidis*.

The prognosis is good in cutaneous blastomycosis, grave in the pulmonary form and usually hopeless in the generalized cases.

Potassium, sodium and ethyl iodide have all been used in the treatment of blastomycosis, but the results of iodide therapy are modified by the immunologic status of the patient. Patients with definitely positive skin tests should be desensitized with vaccine or antigen before iodides are administered, since a failure to desensitize may result in a lack of improvement or even a prompt exacerbation of the infection. Patients with slightly positive skin tests may be successfully treated with large doses of iodides.

Occasionally, instances are encountered in which the patient has no evidence of immunity as indicated by negative skin tests and negative complement-fixing antibodies. These negative findings may result from (1) an excess of antigen in the tissues, as in the case reported by Martin[35] in which the intradermal injection of immune rabbit serum resulted in an immediate wheal reaction, or (2) a total lack of immunity. In Martin's case immune rabbit serum reversed the immunologic processes. Where there is no evidence of immunity, stock or autogenous vaccines should be administered until the patient has complement-fixing antibodies in the serum before the administration of iodides.

X-ray therapy is effective in cutaneous blastomycosis after desensitization of the hypersensitive and while iodides are being administered.

COCCIDIOIDOMYCOSIS

Coccidioidomycosis is an exogenous infection caused by *Coccidioides immitis*. Emmons[36,37] discovered that the infection is endemic in rodents in the arid areas of the Southwest. After the death of the rodent the fungus develops resistant chlamydospores which persist in the soil for an indefinite period of time where they may be introduced into the skin following an injury or breathed into the lungs of man and animals with dust. Davis, Smith and Smith[38] have isolated the organism from the soil.

With the exception of three cases from Italy and four cases from South America, all the other authentic instances of the disease have originated in the Southwestern states.[30]

This disease has been found as early as three months of age and has developed as late as seventy years, but is most prevalent between twenty-five and thirty-five. The progressive granulomatous form of the disease develops most frequently in the deeply pigmented races, such as Negroes, Filipinos, Indians and Mexicans. Laboratory workers may be infected by the accidental inhalation of powdery material from old, dry cultures. Males are more often infected with the progressive disease than females.

The physician should recognize (1) primary coccidioidomycosis which is usually an acute but benign, self-limiting respiratory infection and differentiate it from (2) progressive coccidioidomycosis which is a chronic, malignant, disseminated disease

that involves cutaneous, subcutaneous, visceral and osseous tissues.

The high incidence of positive skin tests to coccidioidin (70 to 80 per cent) in certain areas in the Southwest suggests that most cases of primary coccidioidomycosis either are asymptomatic or cannot be differentiated from mild non-specific respiratory infections.[39–42] Goldstein and McDonald's observations[43] on seventy-five soldiers who developed the primary form of the disease while on maneuvers in the desert showed that the incubation period ranged from one to three weeks. The symptoms were respiratory and the physical findings minimal. After eight to fourteen days skin lesions, usually of the erythema nodosum type (19 per cent), and arthralgia (28 per cent) developed.[43,44,45] This form of the disease has been known for years as "valley fever," "desert rheumatism" or "desert fever." *X*-ray studies showed hilar enlargement, fan-like lesions in the parenchyma of the lungs and occasional pleurisy. Thin-walled pulmonary cavities developed in 4 per cent.[46–49]

The intradermal injection of 0.1 cc. of a 1:1000 dilution of a standardized coccidioidin usually gives a positive reaction after two weeks of illness, and this sensitivity persists for many years.[50] Precipitins and complement-fixing antibodies are absent in mild cases but appear in the more severe infections, only to disappear with recovery.

There is usually an initial leukocytosis, frequently followed by an eosinophilia and accompanied by an increase in the sedimentation rate.

Progressive coccidioidomycosis usually develops from the more severe cases of the primary disease although theoretically it is possible for the infection to originate from an inadequately healed lymph node in a manner analogous to reinfection pulmonary tuberculosis.[51]

The persistence of an elevated sedimentation rate, the development of a high precipitin and complement-fixing titer and the appearance of new parenchymal shadows in the *x*-ray suggest the development of the progressive form of the disease. In a fully developed case, the symptoms, physical signs and *x*-ray shadows resemble those found in cases of reinfection tuberculosis with pulmonary and extra-pulmonary lesions.[52–59]

In primary coccidioidomycosis, *Coccidioides immitis* usually can be grown on Sabouraud's medium from the mucoid sputum although the characteristic spherules are rarely found. (Fig. 3.) The spherules are generally present in abundance in the sputum and abscesses of the progressive form of the disease.

The prognosis usually is excellent in primary coccidioidomycosis and very poor in the progressive form of the disease.

The treatment is symptomatic in the primary infection. The patient should be confined to bed until the temperature, white blood count and sedimentation rate are normal. Persistent thin-walled cavities frequently heal after a period of months but the resistant ones, particularly when complicated by repeated hemoptyses, may have to be eliminated by a lobectomy.[60]

Progressive coccidioidomycosis responds poorly to treatment. Iodides without desensitization are useless and are of questionable value even after desensitization.

HISTOPLASMOSIS

Histoplasmosis is caused by *Histoplasma capsulatum* which is usually found in the cytoplasm of endothelial and mononuclear cells.[30]

The source of the infection has not been found in nature. A few spontaneous infections have occurred in dogs,[61,62,63] but it is probable that these animals, like man, are the victims and not the reservoir of infection.

Occasional cases of histoplasmosis have

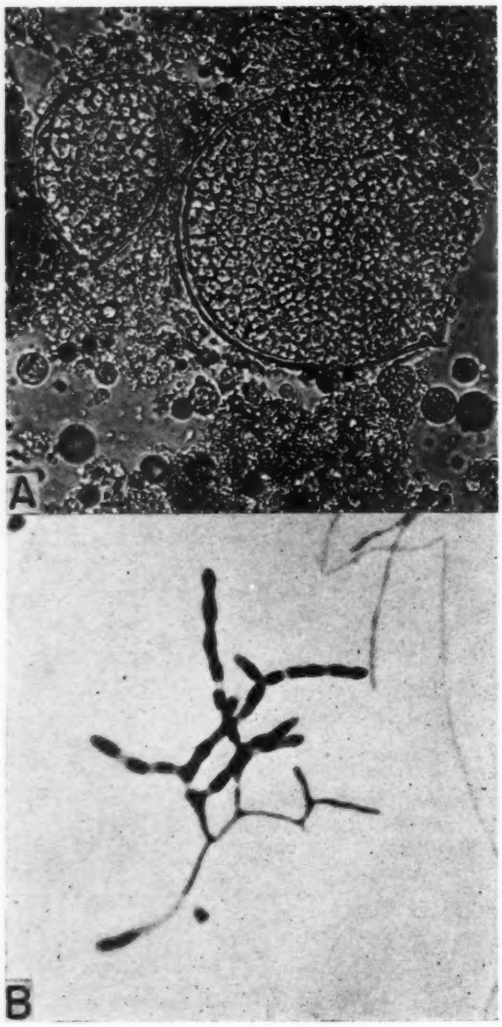

FIG. 3. *Coccidioides immitis*. A, large endospore-filled spherule in pus. × 315; B, filamentous form taken from Sabouraud's glucose agar at room temperature. × 658.

been recognized in widely scattered areas throughout the world although most instances of the disease have occurred in the United States and one-third of these in the states of Michigan, Missouri, Tennessee and Illinois.[64]

Young children are very susceptible to the disease. The youngest patient was one month, and ten other cases have developed in the first twelve months. Both sexes are affected equally up to the age of ten years. After the age of ten, males contract the disease seven times as frequently as females. All races seem to be equally susceptible.

Darling's original cases[65] were characterized by fever, emaciation, anemia, leukopenia, splenomegaly and hepatomegaly. Perhaps this is the syndrome which develops following an invasion through the intestinal tract since De Monbreun[62] has infected young dogs by feeding them cultures of *H. capsulatum*.

A recent review[66] shows that one-third of the reported cases began in the ear, nose, lips, mouth, pharynx and larynx. Enlarged lymph nodes were found in the neck, but hepatomegaly and splenomegaly were inconspicuous or a late development.

The lungs are nearly always involved in the terminal dissemination of the generalized cases, but a primary invasion of the lungs was thought to be a rare occurrence before the recent studies on the origin of non-tuberculous calcification revealed some surprising information. Smith, of California,[67] suggested that the central Mississippi Valley region, where there is a high incidence of pulmonary calcification in tuberculin-negative individuals, might be an endemic area of histoplasmosis. Christie and Peterson[68] and Palmer and his associates[69,70] have shown that there is a close correlation between the occurrence of pulmonary calcification in tuberculin-negative patients and the presence of a positive skin test to histoplasmin. A search is being made in the endemic area for a mild respiratory infection which might correspond to the benign primary coccidioidomycosis in the Southwest.

The intracellular tissue form of the parasite has a superficial resemblance to the Donovan bodies of leishmaniasis. They may be identified in smears of blood, bone marrow, lymph nodes, spleen or in biopsy specimens. The tissue form of the parasite will grow at 37°C. for a time on blood agar or other rich media but soon changes over, particularly at room temperature, to the saprophytic mold-like growth. (Fig. 4.)[71–75]

Histoplasmosis has been uniformly fatal except in a few cases in which the infection has been limited to a small lesion in the mouth.[64]

Treatment is unsatisfactory. Fuadin and neostam have been suggested.[76] Local applications of radium have been used successfully for ulcerations on the tongue.[64]

CRYPTOCOCCOSIS

Cryptococcosis, caused by *Cryptococcus neoformans*, is usually referred to as "blastomycosis" in the European literature and "torulosis" in the older American references.[77,78,79]

Spontaneous infections have been observed in animals, but direct spread from animal to man or from man to man has not been recorded. Benham has isolated from normal human skin[80] cryptococci culturally identical with *C. neoformans* but with slight pathogenicity for animals.

Cryptococcus infections have been encountered in all parts of the world. In this country most of the cases have been reported from the eastern seaboard region and in a zone extending across the southern states from Florida to California.[30]

The disease may occur at any age from ten to seventy years, but is most prevalent between forty and sixty. Males are infected almost twice as often as females, and all races seem to be equally susceptible.

C. neoformans may produce (1) a primary infection of the lungs which simulates tuberculosis or neoplasm,[81] (2) superficial ulceration of the skin with multiple sinuses, as in the original case reported by Busse and Buschke,[82] (3) subcutaneous nodules or abscesses which resemble myxomatous tumors,[83] or (4) a primary meningitis which may be confused with tuberculous meningitis. The organism has a marked predilection for the brain and meninges, and many cases beginning in the skin or lungs terminate with a meningitis.[78,84,85,86]

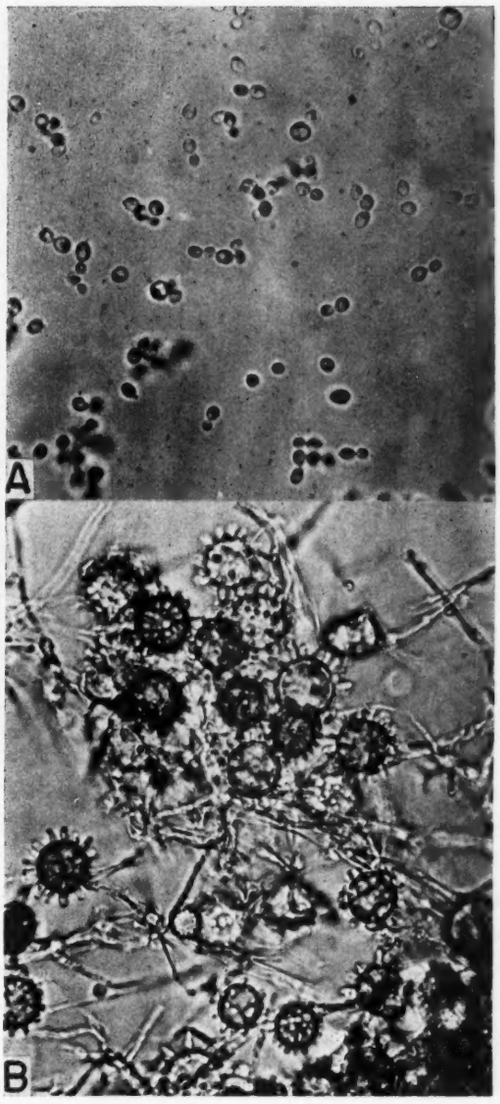

FIG. 4. *Histoplasma capsulatum*. A, yeast-like form cultured on blood agar at 37°C. × 700; B, filamentous form with large, tuberculate chlamydospores from Sabouraud's glucose agar. × 658.

The organism multiplies by simple budding and is characterized by the presence of a large mucoid gelatinous capsule which is easily identified in tissue, spinal fluid or in cultures. (Fig. 5.)

The prognosis is poor in the skin and subcutaneous forms, worse in the pulmonary and practically hopeless in the cerebral and meningeal infections.

Nearly all of the authentic cases of cryptococcosis have terminated in death. Reeves,

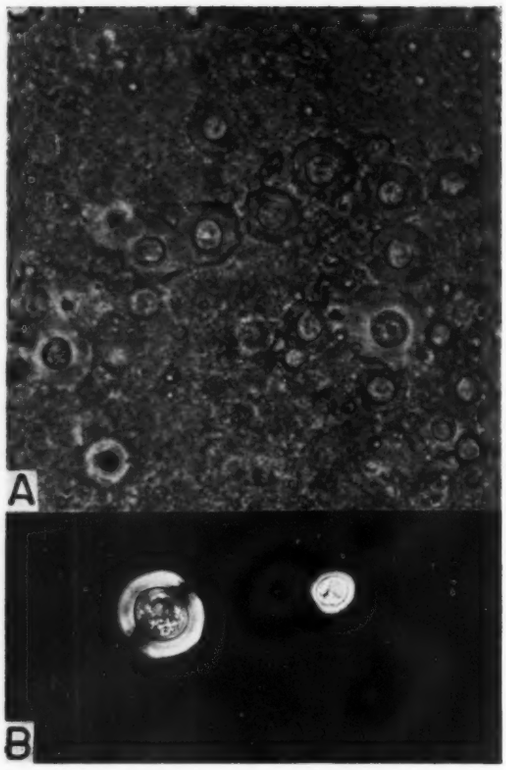

FIG. 5. *Cryptococcus neoformans*. A, in pus. × 684; B, in pus. India ink preparation. × 684.

Butt and Hammack[87] have cured one patient with sulfapyridine, Marshall and Teed[88] another with sulfadiazine. We have seen one case of pulmonary cryptococcosis improve with sulfadiazine and another apparently cured after prolonged treatment with this drug. Recently Jones and Klinck[89] reported a case which failed to improve with sulfadiazine or penicillin. Mice infected with the culture isolated from the patient were not protected by either sulfadiazine or penicillin.

MONILIASIS

Moniliasis, usually caused by *Candida albicans*, is almost certainly an endogenous infection since pathogenic strains have been isolated from the mouth, vagina and intestinal tract of normal individuals.[30]

Moniliasis has been found in all parts of the world. It occurs at all ages, in all races and in both sexes. Occasionally, the infection is contagious, and true epidemics of cutaneous moniliasis have occurred in fruit packers. Balanoposthitis has been observed in the husbands of women with *C. albicans* vaginitis, and cutaneous moniliasis has occurred about the nipples of mothers nursing infants with oral thrush. Moniliasis of the oral mucous membranes occurs most often in infants and elderly people with wasting diseases. Maceration of the hands in water predisposes to dermal and onychial lesions, poorly fitting dentures to oral lesions and diabetes and pregnancy to vaginitis.[90–96]

Bronchitis,[97] pneumonitis,[98–100] meningitis,[101] endocarditis[102,103] and osteomyelitis[104] have all been reported. In many instances the *Monilia* infections are secondary to some more serious condition, but in other instances they are without doubt the primary cause of the disease. In many individual cases the differentiation between primary and secondary invader is almost impossible even with the aid of the laboratory.[97]

In most instances both the budding yeast-like and hyphal forms of the organism can be found without difficulty in fresh wet preparations. (Fig. 6.) Even when the direct examination is negative, positive cultures are easily obtained on Sabouraud's medium or simple agar containing 1 per cent dextrose and adjusted to a pH of 5-6.[105,106]

The localized types of oral, vulvovaginal and cutaneous moniliasis frequently respond readily to treatment, only to relapse when the predisposing factors are duplicated. The chronic types of glossitis and vulvovaginitis may persist for years. Cutaneous moniliasis in hypersensitive patients responds poorly to therapy. Some forms of bronchial and pulmonary infection respond readily to iodide therapy, while others are extremely resistant. The prognosis is hopeless in patients with endocarditis or meningitis.

The dermal and onychial infections should be referred to a dermatologist.

Acute oral lesions respond to simple alkaline mouth washes or a dilute solution of gentian violet. Chronic oral lesions in hypersensitive patients may clear up after careful desensitization. Alter and his associates in the Duke clinic[107] are now obtaining excellent results in chronic cases of vaginitis, which resisted all previous treatment, with a jelly-like preparation of sodium propionate. It is still too soon to conclude that the cures will be permanent.

Bronchial and pulmonary moniliasis usually respond readily to iodide therapy if the patients have not developed a hypersensitivity. When the hypersensitive patient is desensitized and treated cautiously with iodides, the improvement is slow but progressive. Intravenous gentian violet[30,98] has been used successfully in some of the acute pulmonary cases. A rare immunologic type of pulmonary moniliasis recently reported by Hiatt and Martin[108] was cured with immune rabbit serum.

SPOROTRICHOSIS

Sporotrichosis is caused by *Sporotrichum Schenckii* which is primarily a saprophyte or parasite of plants.[109] It has been found in nature on thorns, ferns and the bark of trees. Du Toit[110] isolated the organism from timber and mud in a mine in South Africa. Spontaneous sporotrichosis has been observed in horses, dogs, cats, rabbits and rats. Foerster[111,112] reported two instances of the disease in man acquired by handling contaminated dressings, and Meyer[113] infected himself with a culture isolated from a horse.

Sporotrichosis has been found in all parts of the world but appears to be most prevalent in the north central Mississippi Valley and in France.[30]

The disease has been observed at all ages from sixteen months to seventy-one years. One case out of five occurs in children; males are most frequently infected, especially farmers, laborers and horticulturists.

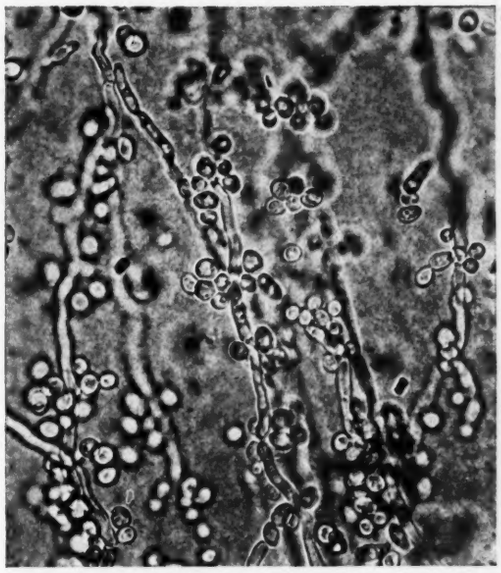

FIG. 6. *Candida* (*Monilia*) *albicans*. From Sabouraud's glucose agar at room temperature. × 658.

A surprising number of cases have followed the prick of a barberry thorn.[112]

According to De Beurmann and Gougerot,[114] the disease may be divided into six clinical types: (1) lymphatic, (2) disseminated, (3) epidermal, (4) mucosal, (5) skeletal and (6) visceral. To these one should add (7) the pseudoneoplastic form recently described by Smith.[115]

The tissue form of the disease is a small, gram-positive, cigar-shaped body which is found in the cytoplasm of monocytes, giant cells and leukocytes. The organisms are rarely seen in biopsies of human material, but appear in abundance when the infected tissues are inoculated into rats. During the past year Campbell[116] succeeded in growing the tissue form of the organism by culturing it on the cystine agar designed by Francis for the isolation of *Pasteurella tularensis*.

The mold-like or saprophytic form of organism grows readily on Sabouraud's medium (Fig. 7) after ten to twenty days' incubation.

The prognosis is excellent in the very common lymphatic forms and the less com-

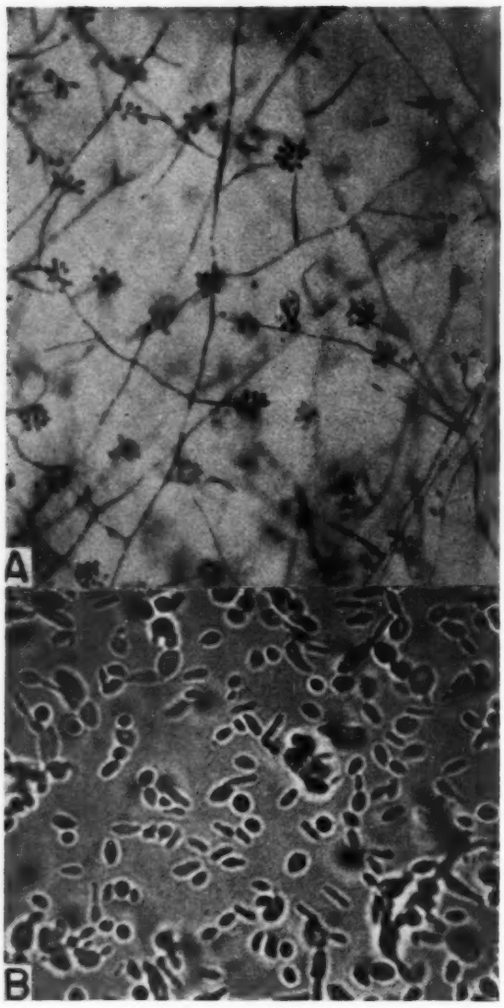

FIG. 7. *Sporotrichum schenckii*. A, filamentous form on Sabouraud's glucose agar at room temperature. × 658; B, tissue form taken from cystine agar culture at 37°C. × 762.

mon pseudoneoplastic type but is poor in the rarer disseminated and visceral infections.[117]

Potassium iodide is practically a specific in the treatment of sporotrichosis, but large doses should be employed and continued for four to six weeks after apparent recovery. An occasional case may require supplementary vaccine therapy.

MADUROMYCOSIS

Maduromycosis is a chronic infection usually of the feet but occasionally of the hands or other parts of the body. It is characterized by chronicity, tumefaction and multiple sinus formation. Identical clinical pictures may be caused by any one of thirteen species of *Actinomyces* or any one of twenty-two species of molds belonging to two classes and nine genera.[30,118]

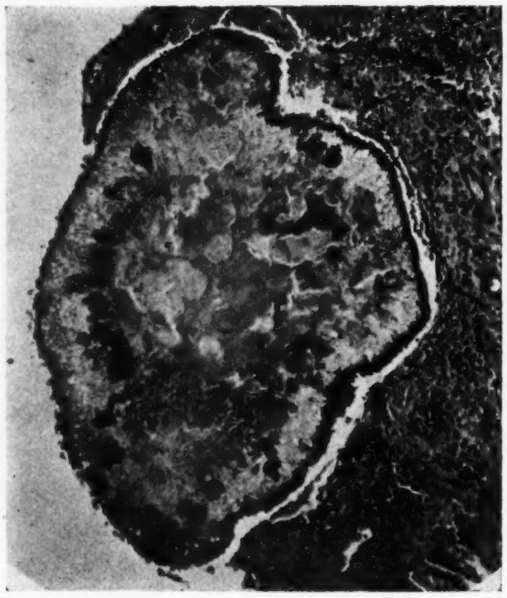

FIG. 8. Maduromycosis. Large granule found in section (case due to *Monosporium apiospermum*). × 112.

The source of the infection is evidently exogenous since more than one-half of the patients give a history of an injury such as a minor scratch, bruise or splinter wound.[119]

The disease occurs most frequently in the tropics and in the southern part of this country.[120,121] The infection may start at any age from eight to eighty, but is most prevalent between the twenty-first and fortieth year. Males are infected nine times as often as females, and most cases have occurred in agricultural workers.

The diagnosis is established by finding the characteristic "grains" in the serosanguineous or "oily" fluid which exudes from the sinuses. The granules may be yellow, white, orchid, red or black, but are not characteristic of any particular type of fungus. (Fig. 8.) About 50 per cent of the cases are caused by the various species of

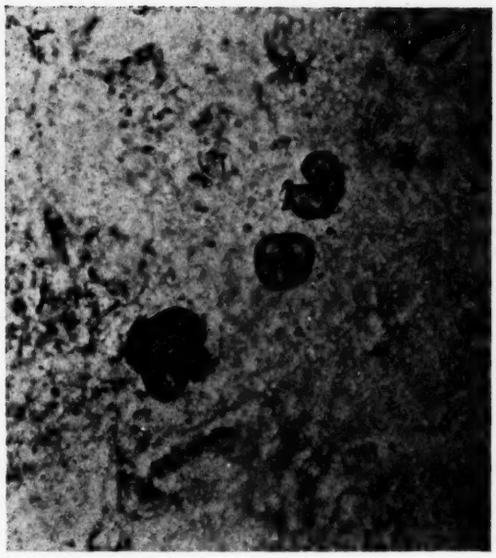

FIG. 9. Chromoblastomycosis. Small, thick-walled, brown bodies found in pus, crusts or section. (Case due to *Hormodendrum Pedrosoi*.) × 816. (W. B. Saunders Co., Manual of Clinical Mycology, 1944.)

FIG. 10. *Rhinosporidium Seeberi*. Sporangium containing spores in section from nasal polyp. × 175. (W. B. Saunders Co. Manual of Clinical Mycology, 1944.)

Actinomyces and the other half by the mold-like fungi.

The prognosis is poor, the patient usually dying of secondary infection.

Maduromycosis caused by *Actinomyces* may respond to sulfonamide[122] and penicillin therapy supplemented by surgical drainage. Those that resist this treatment and all of the cases caused by molds should be treated by amputation of the limb before the patient is debilitated by secondary infections.

CHROMOBLASTOMYCOSIS

Chromoblastomycosis is characterized by the formation of warty cutaneous nodules which develop slowly into papillomatous vegetations. *Hormodendrum Pedrosoi*, *Hormodendrum compactum* and *Phialophora verrucosa* all produce identical clinical lesions.[30,123]

These organisms exist in nature as saprophytes or parasites of wood. Weidman and Rosenthal[124] found that most cases developed following an injury by some form of wood, either living or dead. Conant and Martin[125] proved that certain strains of *Phialophora*, isolated by Kress and his associates from wood pulp, were morphologically and serologically identical with strains of *P. verrucosa* isolated from patients.

The disease occurs sporadically throughout the world and is most prevalent between the ages of thirty and fifty. All races are equally susceptible and males are infected thirty-four times as frequently as females.

The lesions begin as small itchy papules and evolve slowly over months or years without affecting the general health of the patient. The lesions are most often confused with those of blastomycosis or neoplasms.[126]

The diagnosis is established by the demonstration of dark brown septate bodies in pus or biopsy specimens. (Fig. 9.) The mold-like forms of the organism grow readily on Sabouraud's medium.

The disease is almost never fatal, but it is not curable except in its earliest forms.

Complete surgical excision is the treatment of choice for the early lesions.[127] Iodides by mouth and local iontophoresis[128] improves but does not cure the advanced cases.

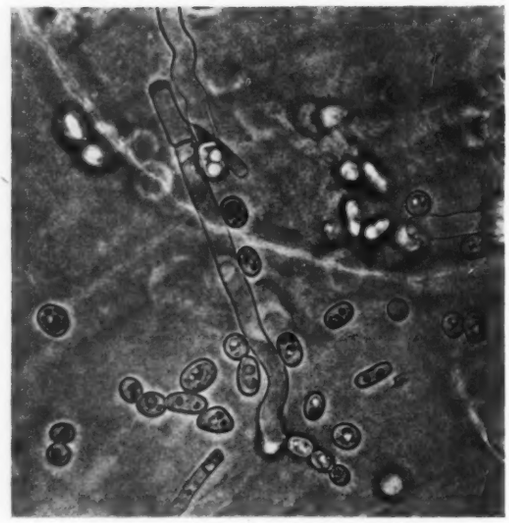

FIG. 11. *Geotrichum sp.* From Sabouraud's glucose agar at room temperature. × 658.

RHINOSPORIDIOSIS

Rhinosporidiosis is caused by *Rhinosporidium Seeberi* which produces friable, sessile or pedunculated polyps of the mucous membranes of the nose, eyes and larynx. Occasionally, lesions develop in the ears, vagina, penis and skin.

Epidemiological studies suggest that the infection is acquired by swimming or diving in stagnant water.[129]

This disease is endemic in India and Ceylon[129,130] but occurs sporadically in various parts of the world, including the United States. The infection is most common in children and young adults. The first thirteen cases reported in this country were all in males.[30]

Both the polypoid form in the nose[131] and the sessile form in the eye[132,133] have occurred in this country.

The diagnosis is established by the demonstration in smears of the round to oval spores, 7 to 9 μ in diameter, or by the discovery in biopsy of the characteristic spore-filled sporangia. (Fig. 10.)

Rhinosporidiosis is rarely fatal, but the patients may succumb to secondary infections.

Complete surgical removal effects a cure. The advanced cases are improved by pentavalent antimony compounds.[129]

GEOTRICHOSIS

Geotrichosis, caused by one or more species of *Geotrichum*, occasionally produces lesions of the mucous membranes which resemble thrush and infections of the bronchi and lungs which simulate other types of mycotic disease.[30,134]

The presence of thin-walled cavities in the parenchyma of the lungs may suggest a clinical diagnosis of primary coccidioidomycosis.[135] In the laboratory, the double-contoured budding cells of the tissue form of the organism may be mistaken for *Blastomyces*, but the accompanying rectangular spores are characteristic and diagnostic. (Fig. 11.)

The prognosis is usually good with iodide therapy.

ASPERGILLOSIS, PENICILLIOSIS AND MUCORMYCOSIS

These molds frequently produce infections in the external ear. Occasionally, granulomatous lesions appear in the skin, nasal sinuses, orbit, bronchi, lungs and other internal organs.[136–144] Squab feeders, fur cleaners and agricultural workers who are exposed to clouds of spores may become infected.[30]

The prognosis is good except for the pulmonary and generalized infections which are frequently fatal.

Iodides are used for treatment but hypersensitive patients should be desensitized.

CONIOSPORIOSIS

A peculiar type of pneumonitis, presumably allergic, occurs in laborers in the northern forests who are repeatedly exposed to the inhalation of spores of *Coniosporium corticale* growing on the inner bark of maple logs.[145]

The patients recover when removed from contact with the spores.

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Seminars on Rheumatic Fever

Rheumatic Fever in the Perspective of Public Health*

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In presenting this subject, I should like to emphasize certain points as a preliminary to what is to follow. First, I am not an expert in rheumatic fever. Second, I shall not be concerned with the question of etiology or the relative importance of heredity and environment; nor shall I go into the question of whether in rheumatic fever and rheumatic heart disease, there is one continuing disease or a series of fortuitous episodes. However, in using the term rheumatic fever I intend to include rheumatic heart disease. Finally, I shall attempt to discuss rheumatic fever in the perspective of public health as a whole, approaching the matter broadly and at first without specific reference to any particular disease. I give you this latter warning because in the text of this paper rheumatic fever itself will not be discussed until a background is sketched in.

Now, in the long and sometimes stumbling history of the acquisition of scientific knowledge, it is noticeable that most progress has been made by those with a singleness of interest and purpose. But it is equally noticeable that knowledge becomes widely useful and usable only when it reaches the stage of simple expression and uncomplicated application. It would seem entirely proper, therefore, that groups of scientists here and there focus their respective interests and research in comparatively narrow fields provided, at the same time, mechanisms are ensured for translating the new knowledge that they gain into applied measures for the benefit of mankind. To do both these things is, ordinarily, quite difficult but in the past few decades, the rapidity with which new fundamental knowledge has been acquired and, correspondingly, the opportunity for its utilization and even the demand for its application have been such as to create a problem of its own. Thus workers in more general fields, and society as a whole, have encountered difficulty in deciding what future emphasis should be given to research in this direction or that, and to what extent efforts in control of one disease or another might and should be undertaken.

To make decisions of this sort is not easy nor can such a choice be made without the hazard of error, because of the multiplicity of causes of ill health and death. Thus, in the manual of the International List of Causes of Death, 200 separate causes are recorded; and in the Standard Nomenclature of Diseases, published by the American Medical Association, and the Manual for Coding Causes of Illness, issued by the United States Public Health Service, there are about 1,000 causes of morbidity listed. It is obvious, of course, that some causes of illness and death are a greater drain upon the public health than others—cancer in

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comparison with German measles, for instance. It is equally obvious, too, that the amount of time or money spent by official and voluntary health agencies in efforts to gain new knowledge or to control various public health problems is not in proportion to the public health seriousness of the various diseases. But it would be unsafe to proceed on the basis of "obviousness" to decide, from a public health standpoint, the relative seriousness of any one of the 200 causes of death or the 1,000 conditions that may cause illness. Some sharper and more objective guide than this is necessary.

Unfortunately, the very nature of the matter under discussion makes it impossible to ensure exact analysis of each of the factors that contributes to the seriousness of any given disease or to weigh these factors. In certain instances, our knowledge and our methods are not sufficiently refined even to discover all the factors that contribute to mortality and morbidity; and even when those factors are discovered, certain human and sociological values and potentials enter so strongly into the situation as to make quantitative expression impossible except as approximations. Similarly, it is not practicable to evaluate all those interacting forces that influence society's decision as to how much time and money might profitably be allocated to any given disease. Nevertheless, it is possible to approach objectively this matter of determining the relative seriousness of disease and, even though complete assay is not attainable, there are at hand certain criteria for judging the relative seriousness of diseases. There are certain others that will bring to light those influences that shape public health practice.

The factors that express the seriousness of a public health problem may be expressed broadly as mortality, morbidity and the age group in which the forces of mortality and morbidity manifest themselves. Each of these elements justifies further discussion.

In attempting to determine the social and even biological burden of mortality from any given cause, it is necessary, of course, that the data from which conclusions are drawn be accurate and complete. One must take into consideration also the accuracy of original observations, the nomenclature and definitions used in the past as compared with the present, the sharpness of diagnosis possible twenty-five years ago and today, and diagnosis in medical center areas as against locations where diagnostic acumen and facilities are not the best. Not only must these factors be considered in relation to the cause of death in question, but also in relation to other causes of death. This necessity is obvious because one must view mortality from a single cause not only in absolute numbers but also proportionately, that is, how much of the total mortality does this single cause bring about. For it would be possible for the number of deaths from a given cause to remain the same, or even for a rate to remain the same, and yet the disease might be of relatively more or less importance than formerly because of increases or decreases in mortality from other causes. One might remain in ignorance of this shift if proportionate mortality is not studied.

If one uses small numbers and data reflecting short experience in considering mortality data, great care must be exercised in interpretation of them lest extraneous influences and chance enter into the picture. Having assured oneself of these safeguards, it would seem reasonable to conclude that, other things being equal, a disease that brought about 25,000 deaths a year and constituted 5 per cent of the total mortality would constitute a more serious public health problem than would one that caused but 2,500 deaths a year and constituted 0.5 per cent of all deaths.

The use of morbidity data as an index of the seriousness of disease must be safe-

guarded by those considerations just set forth in relation to mortality. Similarly, from a community standpoint, one would consider the seriousness of a disease in relation to morbidity somewhat in proportion to the number of cases that occur each year. But, as is the case in considering mortality, there are other factors that must be taken into consideration in relation to morbidity.

The first of these is *case fatality*. It needs no argument to bring out the fact that 1,000 cases of dengue are not nearly so serious as a much smaller number of cases of tetanus. The *length of illness* must also be considered: tuberculosis as against pneumonia. The likelihood of *complications and sequelae* must also be given due weight in evaluating morbidity. Poliomyelitis here would contrast strongly with chicken pox. Rheumatic fever would be weighted heavily both as to length of illness and as to complications and sequelae. *Potentialities for spread* of the disease under study is a factor to be considered in morbidity from acute communicable disease and potentialities of this sort are strongly manifested in such diseases as influenza and smallpox.

The third factor by which one may attempt to obtain some reflection of the public health seriousness of morbidity and mortality from a given cause relates to the age group in which that cause tends to focus itself. One encounters difficulty here in reaching a decision. From a biologic standpoint, and even sociologically, deaths in old persons do not constitute so serious a loss as would arise from the same number of deaths in young adults. However, an attempt to express this loss mathematically opens up many pitfalls. Thus, it has been suggested that biological and social loss in deaths be expressed in terms of the loss of life expectancy entailed. According to this concept, there would be entailed in the death of 100 persons at the age of fifty the loss of some 2,300 life expectancy years, inasmuch as expectancy at the age of fifty is twenty-three. Similarly, 100 deaths at the age of twenty-five would entail the loss of some 4,400 life expectancy years. One might coldbloodedly accept this as a pretty good formula and say that a disease that focuses its effects in the third decade of life is, other things being equal, about twice as serious as one affecting those in the sixth decade. But if such a measurement were accepted, very serious collateral difficulties would arise, for while it is true that the number of years which the average person of fifty may expect to live is twenty-three, this is a general figure. For females, life expectancy at fifty is twenty-five years, males, only twenty-two. Therefore, if one observed such a formula blindly, it would inevitably follow that at any given age the saving of females would take precedence over the saving of males; and inasmuch as the non-white expectancy at a given age is considerably shorter than that of the white, another impossible sociological choice would be presented.

In assaying the relative seriousness of morbidity at the various ages, one can be somewhat more impersonal though not necessarily more accurate in evaluation. Obviously, there is a greater economic loss in the illness of one gainfully employed than in one too old to work. Similarly, the illness of a child entails a less serious economic loss than that of an adult, unless a gainfully employed adult must give care. Further, while the focusing of first attack in children may not entail an immediate serious economic loss, the likelihood of crippling aftereffects in adulthood must be considered. However, in spite of all inherent difficulties in evaluating illness and deaths in terms of age affected, one can proceed fairly safely on the general thesis that morbidity and mortality exerted on children and on the young adult group, is more serious than when focused on older groups, the members

of which have already made their biological and sociological contributions.

As mentioned above, the relative seriousness of a given public health problem is not necessarily reflected in the practice of the typical health agency. Logically, between seriousness of problem and exercise of control measures, there should be a constant ratio. Because this is not the case, it would seem desirable to determine just what influences, quite apart from the seriousness of a given problem, operate in shaping the pattern of public health practice. It would appear that these factors come under one or more of the following headings: (1) the relative amount of scientific knowledge available for the prevention or control of a given disease, (2) the applicability of this scientific knowledge, (3) legal requirements and prohibitions, and (4) public interest and support. Each of these needs further exploration.

As regards availability of scientific knowledge, it may be said that if there is scant knowledge as to how a disease may be prevented or controlled, the activities of the medical profession, the health agencies and the public are not likely to be productive. The health department may proceed empirically and hope for the best, and may make certain gestures under the pressure of legal requirements and public opinion. But if these requirements and pressures do not exist, a health department will ordinarily be most active in relation to those diseases in which clean-cut control measures are available, and least active in those in which scientific knowledge is meager; and this, to a great extent, regardless of the seriousness of the disease in comparison to other diseases.

As to the prevention and control of a given disease, even when scientific knowledge is available there may exist circumstances that interfere with the application of that knowledge. Thus, in certain communicable diseases, *foci may be so disseminated* and masked as to make their discovery and control impossible. This is particularly the case in some of the upper respiratory infections, and in some instances in which animals or insects serve as reservoirs. Another deterrent to application of control measures is that their effective application might invoke a *stringency of action incompatible with the legal rights or freedom of action* of individuals affected. It is, for instance, legally and from a practical standpoint impossible to isolate each person with a cold; and if some fervid anti-vivisectionist caught diphtheria and refused antitoxin because it comes from the blood of a horse, that person could not be forced to take antitoxin. The *cost of an undertaking* might interfere with the application of knowledge. This type of limitation may be illustrated by citing problems in hospitalization or in elimination of malaria through mosquito control.

An *unfavorable attitude by the medical profession* might serve, temporarily, as a deterrent in the application of new knowledge. This is seen occasionally when the health department, acting as an agency of government, undertakes control measures that a local medical profession regards as sociologically objectionable. This occurs most often in the operation of clinics of one sort or another and in medical care of individuals. *Legal requirements* may be such as to force a health department to continue outmoded procedures, or *legal authority might be wanting* for the carrying out of certain obviously desirable procedures. It must never be forgotten that an official health agency must work within the legal framework of the government of which it form as part, and any given health department program must reflect this association.

The discussion of influences that shape public health work, of both official and voluntary agencies, comes finally to a con-

sideration of *public opinion*. One immersed in scientific problems might be inclined to brush this aside as having no bearing on the matter; he might even become exasperated because so unscientific a thing as public opinion is brought into consideration. But regardless of how ill founded the public's opinion might be on one aspect or another of medical and health matters, that opinion, whatever it is, has a very marked influence on the kind and the amount of public health work that is done. Also important to bear in mind in this connection is the fact that public opinion is the net outcome of the interaction of a great many forces and influences. It is, therefore, the part of wisdom to try to discover why the public thinks as it does and how one may best obtain public support for research and practice in any given activity designed to develop new knowledge and better measures for the control of any given disease.

Now, if one applies to rheumatic fever the various criteria that might reflect partly its public health importance, and further inquires as to its present position in public health practice, the results are somewhat disquieting. While an audience such as this is quite familiar with mortality and morbidity data of rheumatic fever, it might still be profitable to restate certain figures that put mortality from rheumatic fever in comparison with deaths from some other causes. Three causes of death with which deaths from rheumatic fever are compared loom large in public health activities: diphtheria, whooping cough and poliomyelitis. From data for the United States in the year 1944 (Table 1), which year was fairly typical, it is found that from all causes there was a total of 1,411,338 deaths: 1,878 of these were caused by whooping cough, 1,145 by diphtheria, 1,361 by poliomyelitis and 27,010 as a part of the rheumatic fever chain of events. When expressed in relation to population, the following mortality rates are derived: whooping cough, 1.4 deaths per 100,000 population; diphtheria, 0.9 per 100,000; poliomyelitis, 1.0; rheumatic fever, 20.4.

Viewed in terms of proportionate mortality, it is found that whooping cough caused 0.1 per cent of all deaths; diphtheria, 0.1 per cent; poliomyelitis, 0.1 per cent; and rheumatic fever, 1.9 per cent.

But these are overall rates and proportions and it is always possible that such crude data may mask important details. Data could be broken down into age, sex, race, geographic locale, economic circumstances, etc. For present purposes no further detail will be undertaken than a separation of deaths under twenty years of age and twenty years of age and older. Proceeding thus, it is found that of deaths from all causes in persons under twenty years of age, whooping cough caused 1,872 or 1.1 per cent; diphtheria, 1,057 or 0.6 per cent; poliomyelitis, 965 or 0.6 per cent, and rheumatic fever 2,248 or 1.3 per cent. Perhaps somewhat easier for comparison are the mortalities from these four diseases expressed as rates specific for the under-twenty group. Whooping cough has an age specific mortality rate of 4.1 death per 100,000 persons aged 0–19; diphtheria, 2.3 per 100,000; poliomyelitis, 2.1 per 100,000 and rheumatic fever 4.9 per 100,000. Expressing somewhat differently the mortality experience with these four diseases in the age group twenty years of age and over, it may be said that for each death caused by whooping cough, diphtheria and poliomyelitis combined, there are about fifty deaths from rheumatic heart disease.

One could go much further in analysis and comparison of mortality from rheumatic fever and other causes, as pneumonia, tuberculosis, cancer, etc., but even from the above and limited consideration, it would seem safe to say that mortality from rheumatic fever is sufficiently great, both com-

TABLE I

DEATHS FROM ACUTE RHEUMATIC FEVER AND RHEUMATIC HEART DISEASE AND FROM CERTAIN OTHER CAUSES, PER CENT OF DEATHS FROM ALL CAUSES, 1944, U.S., AND AGE SPECIFIC DEATH RATES

Age Groups	Deaths*						Per Cent of All Causes					Age Specific Death Rates				
	All Causes	Rheu. Heart Dis.	Polio-mye-litis	Diph-theria	Per-tussis	TBC (all)	Rheu. Heart Dis.	Polio-mye-litis	Diph-theria	Per-tussis	TBC	Rheu. Heart Dis.	Polio-mye-litis	Diph-theria	Per-tussis	TBC
0–9	144,930	655	495	988	1,867	1,892	0.5	0.3	0.7	1.3	1.3	2.8	2.1	4.1	7.8	7.9
10–19	27,491	1,593	470	69	5	2,994	5.8	1.7	0.3	...	10.9	7.2	2.1	0.3	...	13.6
20–29	49,762	1,678	192	23	2	9,715	3.4	0.4	...	...	19.5	8.5	1.0	0.1	...	49.3
30–39	67,465	2,480	120	22	1	9,899	3.7	0.2	...	...	14.7	12.4	0.6	0.1	...	49.5
40–49	116,827	3,346	45	12	1	9,557	2.9	...	...	...	8.2	19.0	0.3	0.1	...	54.3
50 and over	1,004,863	17,258	39	31	2	20,674	1.7	...	...	...	2.1	58.7	0.1	0.1	...	70.3
Total...	1,411,338	27,010	1,361	1,145	1,878	54,731	1.9	0.1	0.1	0.1	3.9	20.4	1.0	0.9	1.4	41.3

Data taken from Vital Statistics of the U.S., 1944, Part 1.

* Corresponding to the following titles of the International List of Causes of Death:

Rheumatic Heart Disease: 58, 90a, 92b, 92c, 93c, 95b
Poliomyelitis: 36
Diphtheria: 10
Pertussis: 9
TBC: 13–22
——: less than 0.05% or less than 0.05 per 100,000.

paratively and absolutely, to indicate beyond doubt that it constitutes one of the very serious public health problems. Additional details may be gotten from Table 1.

But the importance of the problem looms even larger when to mortality there is added the burden of morbidity. Time forbids a detailed comparison of length of disability, economic loss and case fatality from rheumatic fever and from other diseases. Further, morbidity data are not as complete or accurate in rheumatic fever, which is not generally a reportable disease, as in those that are reportable. However, reasonably careful sampling observations suggest strongly that only a few diseases are comparable to rheumatic fever, either in number of cases or in terms of disability, in childhood and in the productive period of life. The disease must, therefore, be weighed heavily in relation to morbidity. However, in spite of these conclusions, measures for prevention, control and care of cases of rheumatic fever occupy only a minor rôle in the health activities of most communities.

In light of the previous discussion of the influences that tend to shape public health programs, what might be the reasons for this seeming neglect? These, it would seem, are not difficult to discover. They are presented, not in endorsement of the situation, but as an analysis of it. In the first place, there is only limited scientific knowledge as to prevention and control of rheumatic fever in the individual or the mass. There is no vaccine or clear cut measure for prevention; there is neither specific therapy to ensure recovery nor any uncomplex procedure to prevent recurring episodes. The next problem is that such measures as are available for treatment involve a somewhat specialized medical skill and rather costly hospitalization. If what is generally believed to be the rôle of the streptococcus in precipitating initial and recurrent attacks (regardless of the question of familial susceptibility) is correct, then the disease falls into the category of one of those with a vast number of undiscoverable and uncontrollable foci.

These are some of the factors that have served as deterrents to more widespread and

intensive work on rheumatic fever in community health programs. But there is another factor which strongly influences the situation. This is that, heretofore, the public interest has not been aroused. Again, it is not difficult to determine why. There is nothing in the disease that, without careful public health education, would appeal dramatically to the public. Perhaps if all cases of rheumatic fever manifested severe clonic spasms, as sometimes seen in chorea, the public would be more impressed; as it is, the damaged heart is beyond public recognition. Not only this, but such overt disturbances as the sufferer might have, occur in the seclusion of his home or at the hospital. All in all then, everything has been against public interest and support of measures for research and control of rheumatic heart disease.

Nevertheless, public interest is an immediate necessity, a first step, if this disease is to be given that attention which its seriousness demands. New knowledge and more productive control and care must, to a considerable extent, wait upon adequate funds; adequate funds, both for voluntary and official health agencies, must wait upon greater public interest and support.

Viewing rheumatic fever in perspective with other public health problems, it seems sound to conclude that quantitatively and qualitatively, it is one of the most serious; that it does not receive from society or society's health agencies an amount of attention comparable to its importance; that the public's interest and support, both directly and indirectly, is not likely to be aroused without the very careful development and maintenance of a program of health education and publicity, nation-wide in coverage, and under the expert guidance of professionals in the field of public relations.

DISCUSSION

DR. QUINN (*New Haven*): Among the diseases that you have mentioned, particularly diphtheria, whooping cough and poliomyelitis, the diagnosis from the clinical standpoint is relatively easy to make. On the other hand, the diagnosis of rheumatic fever is often a difficult matter. Thus in the latter disease, many cases may have been missed and on the other hand, many have been overdiagnosed. On this basis, do you think that the figures that you have given us are comparable?

DR. MUSTARD: I think you are quite right in the statement that rheumatic fever, unless in a dramatic form, is much more likely to be overlooked than whooping cough in its typical manifestations or diphtheria. That would not apply to the subclinical attack of poliomyelitis. We miss a great many of those.

The best data that one can find on relative incidence of rheumatic fever are therefore those that come from the studies made by authorities in that field. Even then we do not have a good population to put these data against.

It is obvious, of course, that it is much more difficult for a general practitioner to make a correct diagnosis than it would be for those who are managing rheumatic fever in an institution like this.

MISS CULLEN: Have any errors been committed in the type and character of education that we have been conducting for the public in the matter of rheumatic fever? It has been said that if the interest of the public is to be aroused in a disease, one must be prepared to offer to the public measures for its management and control. Since we do not have such ready-made methods and since we do not even have sufficient facilities for the care of this acute illness, have we a right to raise the question before the public eye? Is it not true that a great many misconceptions may be transmitted to the public which might create neuroses?

DR. MUSTARD: We are, of course, getting into a difficult field when we attempt to measure the value and harm of education.

I remember once I was up before an appropriating body in a rural area trying to get some money for public health work. There were fifty-two rural magistrates present. One of them seriously jeopardized the situation by expressing the opinion that the country had already been nearly ruined by too much good roads and education. He carried this conviction and prejudice into the field of public health. But I think I understand the basis of your question. When we emphasize to the public the seriousness of a disease and paint a gloomy picture as to what might happen here or there, we are faced with the danger of doing serious psychological injury to the individual who is involved. We must strike a nice balance lest we impose, in addition to his physical disease, some mental distress and handicap.

I do believe, however, that with carefully worked out health education programs, there can be developed, without injury to any one, public understanding and monetary support of public health activities in rheumatic fever.

DR. TARAN: May I qualify the question? It has been said repeatedly that the public may be taken into confidence about disease only to bring the public to the support of the combat of the disease. However, to take the public into confidence as to the severity or the symptomatology of the disease may be very dangerous. This form of propaganda has been tried in rheumatic fever from the point of view of bringing more cases to the clinic, bringing more cases to the doctor somewhat analogous to the campaign for cancer. Thus various brochures and public statements have been made dealing with the symptoms of rheumatic disease. Are we now in a position, with the knowledge that we have about rheumatic disease, to take the public into confidence as to the type of a disease it is?

DR. MUSTARD: I think we should never undertake to develop in the public any responsibility or proficiency in diagnosis. To do so would lead to endless difficulties, apprehensions and disasters. That has been tried, particularly in tuberculosis; and it has been done in cancer, and unfortunate situations have arisen. For instance, by the time that most people develop the advertised symptoms of cancer, they are already pretty far advanced cases. You will notice, too, that tuberculosis publicity is no longer concerned with the man with the thin chest, who is losing weight, who has a cough and spits blood. The emphasis now is that anybody might possibly have tuberculosis, even without symptoms. Generalities with enough punch in them to get action are quite practicable and are to be preferred to either a listing of diagnostic points or scare headlines that arouse the hypochondriac latent in most people. I agree with you that it is unwise to publicize diagnostic criteria.

MISS FEGLI: We have no adequate facilities for diagnosing rheumatic fever today, have we?

DR. MUSTARD: No.

MISS FEGLI: Nor have we adequate facilities for hospitalization of the patient. Under these circumstances, however, do you think we should go in for health education of parents of rheumatic patients?

DR. MUSTARD: I think so far as parents are concerned you should go just as far as you would if you had the facilities you need. I know you are going to question that by asking quite sensibly, "What is the use of getting them all stirred up about going to the hospital when there is no hospital for them to go to." Certainly one would have to adjust advice given parents to the local situation. On the other hand, I am convinced that if we limit our health education of the public in rheumatic fever to such an extent that the public itself does not feel the pressure or, rather, the absence of the facilities that it needs, that public is quite likely to remain smug in the belief that all is well.

It is my belief that the deficiency in community facilities should be emphasized and re-emphasized; and while I should certainly not want to get some mother all worked up about sending her child to the hospital and then be unable to do this, I think we can avoid those immediate situations with some tact. But it would be fatal for us to hold back our public emphasis on the seriousness of rheumatic fever until such time as we have facilities to meet the needs.

DR. QUINN: I would like to ask Dr. Mustard if he has the figures for tuberculosis for this same period in 1944, that is, the mortality figures.

DR. MUSTARD: To get a clear comparison here one must study detail. The total number of deaths reported due to tuberculosis is about twice those reported as caused by rheumatic fever and rheumatic heart disease. Further, if comparisons are made in wide age bands, as 0–19, 20–39, etc., tuberculosis rates will in each instance be greater than from rheumatic fever and this type of heart disease. However, there is one age band in which mortality from rheumatic fever and its associated heart condition is greater than from tuberculosis. This is the group aged five through fourteen years. The respective age specific mortality rates in this ten-year period were 5.7 and 3.8 per 100,000 population in 1944.

SUMMARY

DR. TARAN: Rheumatic fever was discussed in the perspective of public health. It was pointed out that the obvious criteria which shape public health practice are mortality, morbidity and the age group in which morbidity and mortality tend to focus themselves. Applying these criteria to rheumatic fever and rheumatic heart disease, this disease becomes evident as a most burdensome public health problem. Factors which shape public health practice in rheumatic fever as in other diseases were described in detail. The relatively scant scientific knowledge available for the prevention or control of the disease, the difficulties in applying scientific knowledge at hand, legal-sociologic deterrents and prohibitions and lack of public interest and support may be factors responsible for influencing the official and voluntary public agencies from mobilization of their forces in the combat of rheumatic disease. Yet, viewing rheumatic fever in perspective with other public health problems, it was concluded that quantitatively and qualitatively it is one of the most serious; that it does not receive from society attention comparable to its importance; that the public's interest and support is not likely to be aroused without a careful development and maintenance of a program of health education and publicity nation wide in coverage under the expert guidance of professionals in the field of public relations. The education of the public must guard against the creation of hysteria. The aim is to develop in the public not proficiency in diagnosis of rheumatic disease, but rather an understanding of the measures which are necessary to control this illness.

The Rôle of the Medical Social Worker in the Management and Control of Rheumatic Fever and Rheumatic Heart Disease*

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THE rôle of the medical social worker in the management and control of rheumatic fever and rheumatic heart disease can be most clearly described in terms of five activities or functions: (1) Case work services to individual patients and their families; (2) participation in patient management and clinic administration; (3) participation in the development of community resources; (4) medical social research and (5) participation in the teaching of professional personnel.

All of these are important activities through which a distinct and unique contribution to a total program can be made by medical social personnel who are skilled in observing and evaluating social data and are also skilled in relating social and medical data.

It is regrettable that in the field of social work we have been unable to provide such skilled personnel in all of the positions which need qualified workers. The inability of the field to make such provision has led to confusion as to appropriate activity of the social worker, to partially effective social service in many places, and to serious gaps in programs in other places. In this paper I am referring to the rôle and contribution of the skilled medical social worker.

Some Social Aspects of Significance. Before discussing the activities of the social worker in a program for the management and control of the specific diseases of interest to this group, there is value in reviewing some of the aspects of the diseases and the care of patients which have particular social significance. Although both diseases are indeed medical conditions and primary responsibility for prevention, control and care of patients rests on physicians and medical agencies; the social component is significant and substantial responsibility for prevention, control and care of patients rests also on social workers and social agencies. Such responsibility can be demonstrated by four points:

1. Although the specific cause of rheumatic fever has not been discovered, it is agreed that there is an individual susceptibility and that rheumatic fever is more common in some families than others. What emotional and environmental factors are in these two facts about susceptibility is not clear. What is of social significance is that it is also agreed that factors which favor onset and recurrence in the susceptible individual are frequent chilling, damp or overcrowded living quarters, poor diet and conditions leading to lowered resistance.

2. Rheumatic fever is serious because it may affect the heart. Attacks tend to recur and repeated attacks are more likely to damage the heart. If the heart is only slightly

* One of the Seminars on Rheumatic Fever given at the St. Francis Sanatorium for Cardiac Children, Roslyn Long Island, N. Y.

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damaged, the patient may be able to live a normal life; but if the heart is seriously impaired, his activity will be markedly curtailed. Unless recurrences can be prevented, some of the patients will be handicapped persons whose social adjustments, school, employment, family life and personal life are seriously affected. While it is true that physically handicapped individuals can have a wholesome interest in life and enjoy many of the activities of their associates, handicapped individuals frequently need special help in accepting the handicap, in adjusting to it and in choosing activities which are satisfying and in accord with the limitations imposed on the individual.

3. There is no medicine that will cure rheumatic fever although some help, but the treatment during the acute phase and for several months is rest in bed. Rest in bed raises the problem of community resources and personal problems of the individual and family. In only parts of this country are facilities in hospitals available for treatment of the relatively short acute phase of the disease, but in no part of the country are there adequate provisions for the number of patients needing longer periods of bed care, nor for the prolonged periods of convalescence. From the medical point of view, special institutions or sanitariums are considered essential for some patients and desirable for most convalescents. Only in such institutions can the regimen of the patients be as carefully controlled as is deemed wise to protect the heart and avoid such dangers as upper respiratory infections. Such institutions could approach the ideal from the physical standpoint; but from the social standpoint, the continued isolation of the patient from his home and family, the dependence upon others to select his activities for him, the secondary rôle played by parents, the problem of helping the patient and family to readjust to each other and to accept responsibility for the recommended regimen after a year or two of controlled environment are aspects of the management program which have major social and emotional significance.

4. Continued supervision by periodic medical examination is recommended for an indefinite period, with effort made to have the patient return at least once in six months, even though symptom-free. Prolonged and detailed observations are considered necessary in studying the natural history of heart diseases. Also such supervision is considered essential because of the importance of early recognition of the signs of possible renewed activity of rheumatic fever, for continued education of the patient and because of the importance of medical advice on the increase of activity after a period of demonstrated tolerance. This continued medical supervision over a period of years has good psychological as well as physiological effects for many patients, but for some continued supervision is intolerable. For others, the continued medical observation gives tacit proof that they are still ill regardless of what the doctors say and the continued surveillance may arouse anxiety and fear which may result in time in cardiac neurosis and excessive introspection. The prolonged medical supervision which has only positive aims, one of which is to prevent a damaged heart if possible, may be a contributing factor in the making of a cardiac invalid.

These and other social aspects are recognized as existent by medical, nursing and social personnel who work with patients with rheumatic fever and rheumatic heart disease; they are the particular problems of concern to the medical social worker. It is in respect to problems such as these that skilled social service is needed if the program of management and control is to reach its objectives. The use of social work in these programs is described by repre-

sentative persons whom I wish to quote. Dr. Huse, special consultant in Medical Services, U. S. Children's Bureau, wrote with regard to acceptance of the diagnosis and recommendations by the child and his parent: "The medical social worker or the public health nurse or someone else in whom the parents have confidence, such as the priest, may be called on to help interpret the situation to the family. . . . A thorough knowledge of the family situation and great patience and skill in dealing with the difficulties are necessary in order to deal with this type of situation. The State medical social workers have had to deal with many such cases, using not only their own skills but also many sources of information and help within the community."*

In a pamphlet describing state programs for care of children with rheumatic fever, medical social services are described as follows: "The medical-social consultant on the State agency staff is responsible for seeing that any family and environmental difficulties, or the feelings of the child about his condition do not prevent him from following the treatment recommended or getting maximum benefit from this treatment. The medical-social consultant becomes familiar with the needs of individual children in many ways, such as by talking with them and their families in the clinic, during hospital and sanatorial care and at home when necessary. In order to meet these needs, the medical-social consultant helps community social agencies understand the kinds of problems that interfere with adequate care of the child and helps to stimulate development and improvement of the necessary services."†

In a small pamphlet, "Rheumatic Heart Disease in Children," published by the American Heart Association, Dr. Bland writes in a section on treatment, with reference to prolonged bed care and convalescent care, "There are few institutions for this special purpose at the present time and more are needed, but until then much can be accomplished by special heart clinics in our general hospitals. The major part of the work falls upon social service and charitable organizations under the direction of out-patient clinics and interested physicians. In this way satisfactory convalescent care has been arranged for many patients in their own homes, and for others in special foster homes. Not only has it been possible to provide this necessary bed care, but valuable service also has been rendered in making certain that the instructions of physicians are understood by the patient and the family, in securing the cooperation with school authorities for home teaching and special vocational guidance; finally, with the aid of capable volunteer workers, in maintaining the morale of these youthful patients at a surprisingly high level in spite of months in bed in uninteresting surroundings. Such service requires and deserves the interest and support of every community."

The New York Heart Association in its publication, "Standard Requirements for a Cardiac Clinic,"* includes these statements:

"SOCIAL SERVICE

"The following outline is not intended to list all the responsibilities of a cardiac social worker, and includes only those duties indispensable to the operation of the clinic.

"*Major Objectives*†

"The major objectives recognized so far as appropriate to hospital social service are:

"Inquiry into the social situation of . . .

* HUSE, BETTY. If a child has heart disease or rheumatic fever. *The Child*, pp. 163–165, May, 1944.

† U. S. CHILDREN'S BUREAU. State Programs for Care of Children with Rheumatic Fever under the Social Security Act. 1944.

* Published 1936 by New York Tuberculosis and Heart Association, Inc.

† From The Functions of Hospital Social Service Monograph No. 1 of the American Association of Medical Social Workers, pages 62–63.

patients and the reporting of the findings to the responsible physician . . .

"Determining, in collaboration with the physician, the factors in the social situation pertinent to the patient's health . . .

"Setting up, in collaboration with the physician, a possible goal . . . for the patient . . .

"Executing the social worker's part in the plan for helping the patient . . .

"*Responsibilities*

"The social worker shall be present during the entire clinic session and should interview all new patients on their initial visit, and all return patients as necessity demands.

"The social worker shall supervise the return appointments to the clinic, shall keep a record of the visits of individual patients, and shall follow all patients who fail to keep their appointments.

"Patients who have not returned to the clinic for a period of six months since the date of their return appointment shall be visited before being transferred to the inactive list.

"Home visits should be made on all new patients as soon as possible, and the Social Record (No. 4 of the New York Heart Association forms) should be completed not later than three weeks after enrollment.*

"On order of the physician, the social worker shall arrange for the hospitalization or convalescent care of patients.

"The social worker shall be responsible for the transmission of reports concerning cardiac patients to school nurses, visiting nurses, and other social workers.

"When patients are transferred to another clinic or institution, the social worker shall be responsible for sending a transcript of the record.

"The cardiac social worker shall keep a record of active and inactive patients, clinic attendance, readmissions, and social service visits. These records shall conform to the schedules devised by the Committee on Cardiac Clinics, and should be submitted every month to its Executive Secretary. (A sample of these schedules may be secured from the Executive Secretary of the Committee on Cardiac Clinics.)"

* In order to establish a diagnosis a patient is sometimes required to make three consecutive visits to the clinic. In clinics holding weekly sessions, the final diagnosis may not be established until the third week.

These citations from writings which present the problems of rheumatic fever and rheumatic heart disease and the broad programs for care do not make clear, in most instances, the actual services of the social worker. They suggest the general rôle that is played. In the statement of standards by the New York Heart Association, the specific responsibilities in relation to patient management and record keeping are detailed as the statement purports to give only "those duties indispensable to the operation of the clinic." As might be expected, one finds detailed descriptions of the medical social worker's activity in articles written by social workers.*

CASEWORK SERVICES TO THE INDIVIDUAL PATIENT AND HIS FAMILY

Social casework has been variously defined; there are many gradations in its practice. Casework is not synonymous with social work; it is one of the processes used in social work. Stated in terms of process, medical social casework in a cardiac clinic is essentially this: From the doctor the caseworker secures the medical data and the doctor's understanding of the patient and his problem. Through interviews with the patient and possibly one or more members of the family, the caseworker learns much about the patient as an individual—his personality, his social situation, his family relationships, his understanding of his medical condition and his attitudes toward his illness and medical care and toward the limitations which are imposed

* Ebert, Virginia. Case work services to children with rheumatic heart disease. *The Family*, pp. 7–14, March, 1941. Cohen, Ethel. The social component in heart disease. *Am. Heart J.*, pp. 422–430. October, 1938. Terry, Edith. Some social aspects of rheumatic heart disease. A paper given in 1940 in a symposium on Rheumatic Fever and reproduced for distribution by the New York Tuberculosis and Health Association.

on his activity. Through contact with others who know the patient or the family situation, such as social agencies, school teachers and nurses, she may supplement her observations and information and thus gain more understanding of the person and his social situation. The evaluation and analysis of data constitute a diagnostic process which is most effectively done when collaboration with the doctor is possible. The doctor who has examined and studied the patient as an individual with a medical condition and the caseworker pool their findings and their evaluations of their data and together they arrive at a medical social diagnosis. There is value not only in pooling findings and arriving at an accurate medical social diagnosis, but also in joint thinking regarding recommendations to the patient and in sharing treatment plans, at least to the extent that each will understand the part the other is playing in the care of the patient. The caseworker continues study of the patient, just as does the doctor, as treatment progresses. The basis of casework treatment is the establishment of a relationship with the patient (or the parent) that will enable the caseworker to be helpful to the patient in meeting his needs. Through interviews and through mobilization of community resources, if needed, the caseworker continues her service to the patient as long as her services are useful to him or his family. Casework requires professional skill; it frequently requires a substantial amount of time for intensive study and treatment; it is the major activity of most medical social workers in hospitals and clinics.

The content and value of casework can be illustrated better by a case situation than by a description of it as a process:

Jack Martin, aged fourteen, was admitted to the hospital through Emergency Service. The boy had joint pains, a sore throat and a fever of 103°F. Subacute bacterial endocarditis was considered as a possibility but ruled out, and a diagonsis of acute rheumatic fever was made.

Past Medical History. Jack had been under the care of a private physician intermittently for the past seven years. His first attack of rheumatic fever had occurred when he was seven years of age. He was bed fast for a year, but by the time he was nine years old he was up and about all day. However, he got joint pains when he attempted to go to school so he lived on a fairly restricted program of home study and quiet play activities. At the age of twelve, he had returned to school, but a few months later he had a second attack of rheumatic fever, less severe than the first but necessitating bed rest for six months. Gradually he increased his activities, but did not return to school. He believed his present symptoms were due to overexertion, as he was playing basket ball quite steadily for several days before he came to the hospital. He realized this was too strenuous for him but thought he would like to try an active sport for a while.

Medical Care. Jack was kept in the hospital seven weeks, on complete bed rest, before his mother asked to have him discharged against medical advice.

Social data were secured from the mother and patient while the patient was on the ward.

The patient was a dull looking, blond boy whose response was very slow. It seemed as though he did not hear very well because it was always necessary to repeat statements. When the worker introduced herself to the patient on the first occasion, his reply was, "I can't talk about my family. I always put my foot in it. My mother likes to do that and will tell you anything you want to know." He expressed very little interest in the things around him and was quiet. He did express a desire to become a radio mechanic and for that reason was anxious to get well. When occupational therapy was recommended by the doctors, the patient said that he did not think he would like it and that he would prefer not having anything to do. He was not demanding or uncooperative on the ward.

Habits. He usually stayed in the house reading or working on the radio with which he liked to experiment. Usually his activities were re-

stricted to no strenuous sport, but this summer he had participated in basket ball games. At school he was greatly retarded and was not very quick. He had no particular interest in school but was anxious to finish as he wanted to be a radio engineer.

Food Habits. According to the patient and his mother he was on a diet but upon inquiry it was learned that the patient's diet consisted of the foods he liked with the elimination of all the food which he disliked. His favorite meal was a toasted cheese sandwich. The mother had little or no conception of a well balanced diet and had allowed her son to let his food fancies develop to such an extent that his food habits were very poor.

Environment. The patient, his mother and one older brother occupied a four-room apartment on the third floor of a walk-up apartment. The mother stated that it was not a very nice apartment but it was the best that she could afford.

Finances. The income of the family was paid to the patient's mother by the father and was $17 to $20 a week depending on the earnings derived from his trucking business. Because of the small income and the unemployment of the patient's two older brothers, they had left home and were living in the homes of the girls whom they expected to marry. Although the patient's mother did not approve of this, she shrugged her shoulders and said there was nothing she could do about it.

Family Relationships. The patient had a very definite place in the family group and was treated by them in rather an unwise way. His differences from the rest of the family were stressed rather than his assets. There was some question as to how much the patient and his mother were able to understand about his condition. For the past few months the patient's father had not been living in the home and, according to the mother, was not interested in the patient's welfare or in any one else's welfare.

Marital Relationship. According to the patient's mother she and her husband had never gotten along very well and he had always gone with other women and had had several children by them. She showed the worker a letter received from one of these women when she was in the hospital having just given birth to a child of his. The patient's mother stated that she was worried because her husband had told her that he was planning to divorce her in order to marry a young girl who was about to become a mother. If he divorced his wife, she did not know how they would get along because he did not earn enough to support two families and she had no other source of income.

Atmosphere of the Home. It was evident that the home situation was not satisfactory and there was some question as to whether or not this would interfere with the carrying out of the patient's treatment. Evidently the patient's mother discussed the marital situation with the patient at great length and he was familiar with the marital difficulties she had had.

Patient's Mother. The patient's mother was an uneducated woman who had very little idea about looking after her children although she did express interest in the patient. She delighted in talking about the unfaithfulness of her husband and considered herself very brave in putting up with all of his wanderings. She was oversolicitous about the patient.

Social Service Exchange. No record.

Social Worker's Impression. It was believed that the patient may be helped in making his adjustment to his handicap and in understanding his illness. The martial situation had existed in the family for such a long time that it was doubtful if any one from the outside could assist in a solution.

Regrettably, the next notation in the social record is not a statement of case work treatment over a period of seven weeks, but a statement regarding the patient's discharge from the ward:

Discharge Note. Patient's mother preferred to take him home although he should remain here. She believed she could treat him better at home. She had recently moved to an elevator apartment, where the patient would be able to get up on the roof.

The social data noted in the record meets the requirement of a social history as part of a medical study. It does not give evidence

that the social worker carried on any continuous contact with the patient or his mother during this critical period. It does not give evidence of development of a relationship with the boy which make casework treatment possible.

The next entry is seven weeks later, made after a follow-up visit had been made by another worker from the social service department, maybe by a person who was assigned to make follow-up visits. Her entry is as follows:

Home Visit. Because the patient had not returned to the follow-up clinic, a visit was made to the home. The patient's mother had been giving him most devoted care although it had been difficult for her to make the patient obey. The patient's mother was carrying out her own theories of medicine and medical care and stated that she would not bring the patient into the hospital unless the doctors agreed to carry out her recommendations. In addition, although she believed that the doctors knew what was wrong with the patient, she did not believe that they knew how to treat his illness. She had planned to take the patient to another hospital but he had been too weak to be moved. He was running a temperature in spite of the efforts of his mother to bring it down by depriving him of such foods as she believed cause fever. If the patient were readmitted to the hospital, very definitely his mother would be a problem because she would want her ideas about food and care to be carried out on the ward. The patient received good care at home and if the mother was unwilling to bring him back to the hospital it seemed that the best solution to the problem was for him to remain at home.

In a sense, another requirement of a program of management and control had been met: a follow-up visit was made and recorded. The reason for his failure to return is now known. The mother did not want to continue the patient's care in that hospital. That is clear, but what is also clear is that this boy and his mother were not able to handle the boy's illness nor any of his problems in a way beneficial to the boy. Casework treatment was indicated as well as further medical care. Neither was received; instead the boy was placed eventually on the inactive list, with a notation, "Mother prefers care elsewhere." This case record started with adequate medical and social study, but the mother rejected the medical treatment and social casework treatment was apparently not offered. The social history and the follow-up visit in the home do not appear to have been helpful to the patient, to the mother nor to the physician.

Five years later Jack appeared in the clinic. Thus a three-year period of active medical care and casework treatment was begun.

Jack, now nineteen, was underdeveloped and appeared listless. His complaints were frequent colds and a discharging ear. He had not had any more acute attacks of rheumatic fever since he left the hospital against advice five years before. He had gradually resumed activity but at no time had he felt able to return to school. He stated that his usual program consisted of arising about mid-morning, puttering about the house until his home teacher came in the early afternoon, reading and tinkering with his radio in the evening. He seldom went out of the house for more than an hour, usually for a short walk in the neighborhood. He had taken cod liver oil and a tonic when his mother could afford it. His appetite was poor and sometimes he was unable to sleep and read half the night. He sometimes went to the park and to the movie but he "mostly stayed in the house." He had not attempted any sports. "His mother took good care of him," insisting on his remaining in bed when he had a cold. "She fussed when he didn't eat well."

Physical Improvement. Medical examination revealed that he had only slight heart damage. In the cardiac clinic, recommendations were made for gradual increase in activity. He reported faithfully for periodic checks for three years. Medical attention was centered on his continued upper respiratory infections and treatment of the discharging ear. He made

marked improvement in his general physical condition; when he was twenty-two he had been symptom free for a year. He had been employed in a sedentary job for six months.

Social Casework Treatment. Patient's Response: Jack was mildly interested in the worker's suggestion that she might be able to help him work out a program of increased activity as the cardiologist had suggested. He seemed doubtful that he could do much more than he was doing without getting sick again but he expressed discouragement over his progress in his studies. He wanted to "at least get beyond grade school." Gradually he became more talkative and interested in discussing how he felt about himself, his mother, and his activities. He was seen weekly for a few months, seldom missing an appointment. Gradually, appointments were lessened in frequency and during the third year of the contact he was seen only when he came to the hospital for his periodic exam in the cardiac clinic.

Problems as Seen by Jack. He was troubled over his learning speed. His teacher told him "he was intelligent" but he was discouraged. His mother, who was a "quick thinker" thought he was slow and criticized him for his lack of progress. His mother wanted him to be an office worker, but he wanted to be a musician. He thought he had a good voice and possibly could be a radio entertainer if he could afford music lessons. On the other hand, his mother could not afford music lessons, and anyway he thought he should do what his mother wanted him to do. He owed much to her; she had taken good care of him and he "ought to want to do as she wished—he owed her that much." He felt he was slow in everything. He did not believe he could get up in the morning and get to school, "even if a school with an elevator could be found." (The doctor had given permission for stairs and the patient still lived in a third-floor apartment.)

He felt he had to get to the place where he could support his mother soon; she had been "supporting him too long" on the small income from the father.

His mother urged him to eat heavily but he was afraid of "getting fat like his mother, although being overweight was all right for older persons." He was "not unhappy at home all day." He had not "kept up with his friends" but "that was the way it was when you have a bad heart." He wanted to "make up for his illness somehow." This wish to "make up for his illness" seemed mostly centered toward making it up to his mother who had sacrificed so much to take care of him.

Mother's Attitude. His mother at first accompanied him to the clinic but gradually came less often and by the end of the year, Jack was coming to the clinic alone. She was an energetic, opinionated woman who continued to have definite ideas about Jack's treatment. She believed she knew better than anyone what diet he should have and what medicine he should be given. She prided herself on giving him the most expensive eggs, milk and chicken which were procurable. She talked about him as a child. She could not understand his confidence in the doctors as she did not have any, but he wanted to come. "She saved Jack's life five years before when the doctors gave up treatment for him." By dint of "hard nursing, she had brought him through." In his mother's presence, Jack sat slumped in his chair and failed to respond to her enthusiasm over his gain in weight. As Jack became more expressive about activity he wished to attempt outside the home, she became critical of his "independent notions," saying he "did not like her ideas any more."

Personal and Social Progress. Through regular interviews and establishment of relationship with both the mother and boy at first, then less often with the mother, the worker was able to help Jack try increased activities outside the home. He gradually began to take more responsibility for his own activity. He also began to wonder whether his colds were "mental." He liked to feel chilly and would sit by the open window or go outdoors without his coat unless his mother caught him. "She bundled him up too much." Gradually, he accepted more responsibility for dressing in accordance with the weather, without the nagging of his mother.

The worker arranged for him to have a voice test as part of the exploration for a vocational choice. On the basis of the test, Jack was willing to consider that music would be an avocation and lessons were arranged for at a settlement

house. Since he was too old to return to the public school to complete the eighth grade, a volunteer part-time teacher was secured to help him prepare for an examination for graduation from elementary school. After completing this period of study, the social worker helped him explore vocational possibilities and referred him to an agency which provided counselling, training and placement of the handicapped. He was given training in crafts and was later placed in a craft shop.

To find friends and undertake social activities was the hardest step for him to take. As he began to recognize that he was not really a "cardiac cripple," he was in conflict about social contacts. He realized that all his former friends and the boys in the neighborhood thought of him as having a bad heart and they had long ago stopped asking him to do anything with them. He felt "inexperienced" with boys of his own age and unwanted by younger boys. A series of community resources were used by the social worker in helping him find companions. Arrangements were made for attending a craft class at a settlement house; camp placement was secured for several summers at a camp that offered a wide program so that he did not feel the need to compete with the more active boys. He continued to be slow in accepting the doctor's recommendations for increased activity but after he had encouragement to try new things he expressed satisfaction in a more varied program.

While he was away at camp the summer he was twenty-one, his mother died suddenly of a stroke. The worker helped him adjust to this loss through close contact for a month. He was depressed over his loss and felt it was particularly hard to bear because the next month he was to begin his paid work at the craft shop. Feeling greatly indebted to her for her devotion of years, he also was somewhat relieved to be free of her growing dependence upon him. His brothers were all married and lived out of the city so his mother had concentrated all of her attention on him. He had considerable guilt over his sense of freedom, but was able to write his father that money need not be sent any longer as he had a job. The worker helped him find a boarding house where two other young men lived.

At twenty-two he still had a slightly damaged heart and was a shy young man with only a start made in his social adjustments, but he was not the listless boy of nineteen who lived as a cardiac cripple.

DISCUSSION

DR. TARAN: Miss White's lucid and thoughtful presentation of the rôle of the social worker in the management of rheumatic disease is now open for discussion.

MISS BEGLEY (Nassau County Tbc. Assn.): In the management of the case which you presented, it would seem that the boy has been completely under the influence of the overattentive or "neurotic" mother. What rôle did the school authorities play in the management of this case? The case history gives me the feeling that the mother of this child needed psychiatric treatment as much as the child needed medical follow-up. Who would be responsible for the education or treatment of the mother of the child?

MISS WHITE: This boy was under the care of a private physician until he was fourteen; hence the hospital record does not have information as to the rôle the school authorities played. The nurse, school teacher or anyone coming into professional contact with the boy had a responsibility to size up the problem and to consider what help the mother could use.

MISS NEIL: Do you think that more visits on the part of the social worker before the patient became an adult would have changed the course of the disease?

MISS WHITE: The medical social worker, by making more home visits when the case was first known, could have offered more casework service. It is obvious that unless more detailed study is made in an individual case, the influence of the social worker upon the course of the disease will be small.

One home visit was made and the case

was closed. A person's interest in care cannot be definitely decided on one visit. I wish we would not be so quick with "closing a case." Unfortunately, this seems to be the present procedure in some places, possibly because of the great load of cases that the social worker carries. I do not believe in partial social workers' service any more than I believe in partial medical care.

Miss Fitzsimmons (Long Island College Hospital): Do you think that the relationship of the social worker to convalescent homes and sanatoria should be closer than it is at present? It would seem to me that if the parents of the patient are to be prepared for the return of the child after he has sanatorium or convalescent care, that the social worker should be more closely acquainted with the progress of the case at the sanatorium or convalescent home.

Miss White: Definitely. We cannot say that just because the patient has been transferred to an institution where the care may be excellent, the responsibility of the social worker in planning for the child has ceased. Possibilities for service by the social worker begin with the first acquaintance with the patient and continue throughout the course of his illness and as long as the patient may be followed. This is particularly true in a disease like rheumatic fever and rheumatic heart disease.

Miss Danzinger: Is there a trend toward separation of casework and follow-up work?

Miss White: I do not know of such a trend. The important question is one of use of personnel. We have to be practical in terms of distribution of responsibility among the available personnel. How are we to divide the time of a social worker between casework and follow-up? If a social worker makes fifteen follow-up home visits a month, there should be time not only for second follow-up visits if necessary, but time also for casework with those patients. Unless the caseworker has time to carry on with casework treatment, the use of her time for follow-up is not only expensive but results in ineffective use of her skill. If follow-up visits are not to be supplemented by casework service, a clerk might as well be sent. It would seem that we had better do careful work on half as many cases, rather than to follow up many cases without casework service.

Dr. Taran: From the point of view of the social worker, where does the line of demarcation lie between the function of the social worker and the psychiatrist in the management of a rheumatic patient? We have now come to believe that rheumatic fever is a protracted disease of many years' duration, fluctuating between short explosive phases and long subacute protracted phases. The physician who is in charge of a case of rheumatic disease knows from the very onset of the disease that many sociologic and psychiatric problems will arise during the course of this patient's life, because of the protracted nature of this disease. For example, he knows that a child between six and twelve years of age who suffers from repeated recurrences of rheumatic fever will spend a good deal of time in the wards of hospitals, and will not therefore follow psychologically the normal childhood course of development. Both educational and psychologic problems arise during this period. The physician also knows that if this child develops severe cardiac damage he will be handicapped not only in his physical development but also in his sociological adaptations. When such a child has reached adult life, he will most likely be kept from the usual ways of earning a livelihood, and therefore develop rather profound emotional disturbances. The physician further recognizes that this rheumatic patient, if his cardiac damage is progressive and severe, will, in addition, develop a painful cardiac neurosis.

Many of these sociological and psychological disturbances can undoubtedly be modified when handled properly at the right time. What rôle does the social worker play and where does her work and the psychiatrist's work begin in modifying the course of events in the natural history of the disease?

Miss White: I think that social workers come in at all of these stages, but with a different type of service than the psychiatrist. For example, when a child's life is threatened, medical treatment takes predominance over everything else. On the other hand, during the same period of time, the social worker may begin to develop a relationship with the patient upon which she can build later on. I believe that it is during this acute "medical" period that the social worker's job is to develop a proper relationship with the parents of the patient and perhaps also his siblings. We know that not only the patient will need assistance, when he recovers from the acute stage, but also attention to his immediate environment at home may be needed. When the patient gets ready to be mobilized into his social sphere, that is the time when the social worker can do much in helping him with these adjustments. When the patient develops emotional disturbances of a profound nature, the social worker must realize that this has become a psychiatric problem and encourage psychiatric treatment. I do not believe than many social workers are confused as to where our work ends and the psychiatrist's work begins. When the social worker does not realize where her function ends and the psychiatrist's begins, her training is deficient.

It must be admitted that from time to time, the social worker invades the territory of the doctor, the nurse or the psychiatrist. This is done not because she does not realize her function nor because she ignores the value of the nursing or psychiatric services, but simply because of the fact that many programs are inadequately staffed. The tendency to do each other's job is of necessity, rather than choice. If a social worker must fill the gap for the doctor, nurse or psychiatrist, at least she must keep clear in her mind what she is doing and why. If we do that, there will be less confusion. I am convinced that from time to time it is a good plan for physician, nurse, social worker and psychiatrist to get together and to pool and coordinate their thinking. Until the personnel problems are solved, there will be a great deal of overlapping and filling in for each other.

Dr. Taran: I remember a statement by Dr. L. F. Barker at one of the meetings of the Academy of Medicine. He said that he thought that prevention of rheumatic fever was impossible because there was no clear demarcation between the function of the doctor, the nurse and the social worker. He cited the following example: The doctor stated that one way to prevent rheumatic fever is to avoid chilling, and the way to prevent chilling is to wear an overcoat and rubbers. In this instance, the patient was a boy who did not like to wear an overcoat and rubbers. The nurse was sent out to insist that the rubbers and overcoat be put on because the doctor ordered it. The social worker sang the same tune as the nurse, but told the boy that he must wear the overcoat and rubbers not only because he was ordered to do so but because it was good for him. This, of course, did not convince the boy that he must wear his overcoat and rubbers, and therefore, we have no way of preventing a chill. Thus, the boy got a rheumatic recurrence.

Miss White: Perhaps it would be more profitable if the social worker, who understands that the prevention of chilling is important, should try to find out why it is that the boy does not care to wear an overcoat and rubbers. This may be the quickest

approach to convincing the boy of the necessity of wearing these clothes.

MISS STROBACK: You spoke a good deal of the need of having a complete picture of the personality of the child. I was wondering how and for what purpose we are to use this complete personality study.

MISS WHITE: Through a study of the personality of the child the caseworker understands his problems and how to establish relationship with him so that she can help him in the various adjustments he must make to his illness and to the restrictions on his activities. She needs the knowledge of the individual's personality to give casework treatment. We have gone a long way in understanding how to use these personality studies. Perhaps some day we are going to find a short cut for the long case history, but I would not look for it at the present time. I believe that the social worker not only must understand the disease, its natural history, its symptomatology, but must also have a keen insight into personality traits and types.

DR. TARAN: You mean, therefore, that the social worker must be a good doctor and an excellent psychiatrist.

MISS WHITE: No, I did not mean that; she must be a good social worker.

SUMMARY

DR. TARAN: The rôle of the social worker in the management and control of rheumatic fever was discussed. It was pointed out that in order to attain the best results, the social worker must play a specific rôle in the general management of the patient suffering from rheumatic fever and rheumatic heart disease. Since the disease is often protracted and frequently leads to severe crippling cardiac disability, careful study and follow-up of the patient and his environment are necessary if the course of the disease is to be influenced favorably. The social worker does not invade the territory of the physician, the nurse or the psychiatrist, but rather deals with those elements in the management of the case which are sociological in nature. The personality of the patient plays an important rôle in the progress of his disease. The relationship of this personality to social environment must be guided by the social worker in such a manner as to create a sensible and practicable adaptation of the patient to his disease, and of his environment to the patient.

It was pointed out that the line of demarcation in the work of the social worker is clear. Trespassing into fields not definitely within the domain of the social worker occurs partly because there is, as yet, little appreciation of the rôle of the social worker in the management of this or other diseases. In most instances, dislocation of the function of the social worker is due to an inadequacy in clinic personnel rather than to confusion as to the field in which the social worker is to operate.

Conference on Therapy

Treatment of Some Chronic Muscular Diseases

THESE are stenographic reports of conferences by the members of the Department of Pharmacology and of Medicine of Cornell University Medical College and New York Hospital, with collaboration of other departments and institutions. The questions and discussions involve participation by members of the staff of the college and hospital, students, and visitors. A selected group of these conferences is published in an annual volume, Cornell Conferences on Therapy, by the Macmillan Company.

DR. HARRY GOLD: The topic of the conference today is the treatment of some chronic muscular diseases. The opening remarks will be made by Dr. Milhorat.

DR. ADE T. MILHORAT: The voluntary muscles comprise about two-fifths of the total weight of the body and are subject to a wide variety of abnormalities of function and structure.

The incidence of the chronic muscular diseases is unknown. Reliable data on this point are lacking. Our experience here at the New York Hospital justifies the opinion that certain of these disorders, namely, progressive muscular dystrophy and progressive muscular atrophy, occur as frequently as many other conditions with which the practicing physician is familiar. Regardless of their actual incidence in the community, I should like to emphasize that to the individual patient the incidence is 100 per cent and is of serious consequence, for many of these disorders are incapacitating and progress ultimately to a fatal outcome.

MYASTHENIA GRAVIS

This condition is characterized by weakness and fatigability of the muscles. While any of the voluntary muscles may be involved, those earliest and most severely affected are the muscles of the face and throat. Thus, among the most frequent early symptoms are diplopia, ptosis, facial weakness, nasal speech and later, difficulty in swallowing with regurgitation of fluids and an accumulation of saliva in the mouth. In advanced stages, paralysis of the respiratory muscles is a serious complication and may be the immediate cause of death.

Except in the rapidly progressive forms, the course is chronic with fluctuations in the severity of symptoms from time to time. It is often difficult to determine the prognosis in any given case. In many instances, the muscular weakness and fatigability increase over periods of months or years until finally the symptoms are refractory to all types of treatment. On the other hand, some patients improve spontaneously without any known reason and remain relatively or even entirely free from disability for many years. Obviously, the periods of exacerbation and remission of symptoms make it difficult to evaluate the therapeutic measures.

In any therapeutic regimen, the first consideration is rest. The effect of muscular activity induces or increases weakness, and conversely, the beneficial effect of rest on muscular function is often striking.

In many respects, the clinical picture resembles that of curare poisoning in which either neostigmine or physostigmine may promptly abolish the muscular fatigability and weakness. It is, therefore, perhaps not surprising that the drug of choice in the management of myasthenia gravis is neostig-

mine, often referred to under the proprietary name, prostigmine. Neostigmine can be administered orally, subcutaneously or intramuscularly. When given parenterally, the methylsulfate salt is used; the average dose is 0.5 to 1.0 mg. Following subcutaneous or intramuscular administration, definite effects are noted in many patients within a few minutes. Maximal effects are usually noted in about fifteen to twenty minutes and persist for about an hour and a half, after which they gradually subside. Usually the patient's symptoms have returned to their previous status after a period of from two and one-half to three hours following the administration of the drug. Oral administration is the method preferred in the management of ambulatory patients and those in whom disability is moderate. For this purpose, the bromide salt is used, commonly in doses of from 15 to 30 mg., three times daily. In its effect on muscular function an oral dose of 15 mg. is approximately equivalent to a dose of 0.5 mg. given subcutaneously. However, improvement occurs more slowly after oral administration; one-half hour or even longer may elapse before an appreciable effect is noted. Obviously the dosage must be adapted to the needs of the individual patient. As a general rule, the amounts of drug and the intervals between doses should be so adjusted as to provide maximal therapeutic effects without inducing the relatively refractory state that can be induced by excessive doses. It is a common experience that excessive doses of neostigmine usually are followed by exacerbation of muscular weakness and an increased need for the drug. This phenomenon may be explained in part by the pharmacological effect of large amounts of the drug on either the muscle or the motor nerve endplates.

While most patients are able to tolerate relatively large doses of neostigmine, undesirable side effects are occasionally observed. These include dizziness, pallor, sweating, nausea, vomiting, abdominal cramps and tachycardia followed by a slowing of the heart. They may be prevented or abolished by the oral administration of atropine sulfate in doses of about 0.6 mg. two or three times daily. While the side effects of neostigmine are readily antagonized by atropine, its effects on striated muscle appear to be little, if at all, influenced by this drug.

The effect of neostigmine is commonly considered to be due to its anticholinesterase action, that is, neostigmine inhibits the enzyme that hydrolyzes or destroys acetylcholine. However, experimental evidence indicates that the effect of neostigmine in myasthenia gravis can be due only in part to this mechanism and that neostigmine probably has, in addition, a direct action on the muscle fiber itself.

Physostigmine is less effective than neostigmine. Moreover, undesirable side effects occur more frequently after physostigmine, so that this drug is much less useful than neostigmine in the management of myasthenia gravis.

Patients who are seriously ill with myasthenia gravis often require increasing doses of neostigmine. It appears that the muscles of such critically ill patients become increasingly refractory and require increasing stimulation for their contraction. In such patients the effects of the drug are slower to appear, are less pronounced and persist for shorter periods of time than in patients who are only moderately ill. In some fatally ill patients the subcutaneous administration of 0.5 mg. of neostigmine methylsulfate every twenty minutes may be necessary to prevent complete respiratory paralysis. Recurring respiratory paralysis may require that the patient be placed in a respirator. While in some instances this might conceivably be a lifesaving measure, our experience with the respirator has been disappointing.

A serious complication that requires at-

tention is the accumulation of large amounts of viscid saliva. This may interfere seriously with respiration and should be removed frequently by aspiration.

Severe exacerbations of symptoms are often precipitated by acute infections of the respiratory tract. When the intercurrent infection can be treated satisfactorily with antibiotics, or when the patient can be helped to survive until the infection has subsided, the immediate prognosis may be fairly good. However, if the increase in myasthenic symptoms has been of gradual development and without a precipitating cause that can be successfully treated, the prognosis is grave.

Other drugs that have been used are guanidine and potassium chloride. I have never observed any beneficial effect of guanidine. Only the occasional patient is able to tolerate potassium chloride or obtain any beneficial effect on the muscular symptoms.

The frequent association of a persistent thymus or thymic tumor with myasthenia gravis has long suggested a causal relationship between the two conditions. The incidence of thymic changes in myasthenia gravis is not known and such figures obviously depend on the care with which the thymic area is studied. However, it may be said that in about 50 per cent of our cases and those reported by others there is a hyperplastic tumor or persistence of the thymus. Thymectomy for treatment of myasthenia gravis has been performed in several clinics. While the reports differ with respect to the number of cases, the types of patients and the methods of management, the following conclusions are justified: 10 to 25 per cent of these patients may be considered to have been cured; 20 to 30 per cent were much improved; another 20 to 30 per cent were moderately improved and 7 to 35 per cent showed no improvement. About 15 per cent of the patients died during the early postoperative period, and 5 to 7 per cent have died since the operation was performed. Because of the high operative mortality, this form of surgical treatment has been discontinued in some clinics. In general, the results seem to be better when the operation is performed relatively early and in patients with only moderate disability.

Irradiation of the thymus is perhaps of benefit in the occasional patient. However, the spontaneous tendency to exacerbation and remission of symptoms makes it difficult to evaluate any type of treatment until a large series is followed for a long time.

MYOTONIA CONGENITA (THOMSEN'S DISEASE)

This condition is characterized by an inability to relax the muscles promptly after an initial forceful contraction. Usually it is present from childhood and persists for life. Myotonia has no effect on the normal life expectancy of the patient except when the inability to make bodily movements rapidly may involve the subject in an accident. Since muscular wasting and evidence of other structural changes are absent, the management is limited to measures that diminish or abolish the delay in muscular relaxation. Quinine, given as either the hydrochloride or the sulfate in doses of 0.3 Gm. two or three times daily, often accomplishes this purpose. On the other hand, some patients require as much as 0.6 Gm. of the quinine salt three or even four times daily. When these larger doses are taken, the well known side effects, such as diminution of hearing, tinnitus, visual disturbances and dizziness, frequently limit the usefulness of quinine and many patients consider them more disagreeable than the myotonia. Such patients often limit the use of quinine to special occasions when it is particularly important to be relieved of myotonia. The effect of quinine in myotonia congenita is

probably related to an antagonistic action of the drug on cholinergic stimulation. This opinion is supported by the observation that drugs with cholinergic effects, such as neostigmine, increase the myotonia. Although this effect of neostigmine on myotonia can be prevented or abolished by atropine, atropine is without value in the management of myotonia congenita.

Other drugs affecting myotonia are quinidine, the effects of which resemble those of quinine, epinephrine which improves the condition in some patients but is without effect in others and calcium which when given intravenously produces slight but demonstrable diminution in the delay of muscular relaxation. In this clinic, drug therapy is limited to quinine.

MYOTONIA ATROPHICA

In contrast to myotonia congenita, in which a disturbance in the function of the muscles is the only clinical feature, myotonia atrophica may present a number of symptoms referable to various organs. In myotonia atrophica, in addition to the myotonia one finds progressive muscular wasting, lens opacities of the type seen in endocrine disturbances, frontal baldness, a low basal metabolic rate sometimes associated with high levels of cholesterol in the blood, and in males, testicular atrophy. The course is insidiously progressive.

At the present time treatment consists only in the management of myotonia with quinine in a manner similar to that in myotonia congenita. Many clinicians prescribe thyroid for the low basal metabolic rate, but this medication is of doubtful value. Various measures, including testosterone and pituitary extracts, have been used but without significant benefit. In general, it may be said that the management of myotonia atrophica is symptomatic and directed mainly toward the control of myotonia. It has little reference to the underlying pathological process and does not significantly alter the progressive course or the ultimate outcome.

FAMILIAL PERIODIC PARALYSIS

This syndrome is characterized by periodic attacks of flaccid paralysis. The attacks vary considerably in their extent and severity. Occasionally only one or two of the extremities are affected. In other instances, practically all of the voluntary muscles are involved. Functional disability varies from moderate weakness to complete paralysis with the muscles refractory to all types of stimulation. During particularly severe attacks, respiratory and cardiac involvement may occur. The attacks are associated with low levels of serum potassium. There is no constant level of potassium in the blood at which the attacks occur; usually the decrease amounts to 25 or 30 per cent. The low serum potassium levels are not due to the loss of potassium from the body but to its redistribution in the tissues.

Attacks can be terminated by the oral administration of potassium. We use potassium chloride in a single dose of 5 Gm., repeated in fifteen to thirty minutes if necessary. We prefer the chloride to the bromide salt because of sedative effects of the bromide which are sometimes undesirable. Recovery from paralysis often begins before the level of serum potassium is raised perceptibly, probably due to diffusion of the administered potassium into the muscles. Recurrences can be prevented in many patients by ingestion of from 2 to 4 Gm. of potassium chloride daily. Since the attacks usually have their onset in the early hours of the morning, the potassium sometimes has to be given at about 2 A.M. In other instances, administration before retiring is satisfactory. The ingestion of large amounts of carbohydrate, diuresis induced by copious drinking of water and the administration of epinephrine, ephedrine and insulin may

lower the serum potassium levels and thereby induce attacks of paralysis. These should be avoided as much as possible in the management of periodic paralysis. Some clinicians have expressed the opinion that the administration of thyroid and thiamine chloride are of value, but there is little evidence to support this view.

AMYOTROPHIC LATERAL SCLEROSIS AND PROGRESSIVE MUSCULAR ATROPHY OF THE TYPE KNOWN AS CHRONIC PROGRESSIVE ANTERIOR POLIOMYELITIS

No method of management has been demonstrated to have any appreciable influence on the progression of these conditions to a fatal outcome. Various measures have been tried, including the administration of all the known vitamins. One group of workers has claimed favorable results when large amounts of vitamin E were given, but their claims remain unsubstantiated by others. It should be remembered that on the basis of experiments in animals and clinical observations in patients, these syndromes probably result from a variety of causes including infections and deficiencies. Therefore, the basic etiology and hence the therapeutic results in one series of patients might not be duplicated in another series. Clinical improvement has been reported so rarely that satisfactory treatment of patients with these disorders must await increased knowledge. This applies also to muscular wasting of the type known as progressive peroneal muscular atrophy (Charcot-Marie-Tooth disease).

Recently, Mr. Solomon Friedland, a biologist, suggested the use of cytochrome C in a particular case of amyotrophic lateral sclerosis. We had previously tried a long list of other preparations, all of which were without any effect on the symptoms. We have now given cytochrome C intravenously to this and to three other patients in doses of 50 mg. daily. The effect of this preparation is still being studied in these four subjects, as well as in others with different types of muscular disorders. It is much too early to make a statement on the ultimate value of this material, but so far, the effects are sufficiently striking in this otherwise unresponsive condition as to merit comment. We have noted significant improvement in muscular function, which we are inclined to attribute to relief of the spasm and to an increase in the strength of the partially denervated groups of muscles. The improvement is most evident in the muscles showing only slight wasting, less in those moderately affected and practically or completely absent in the muscle groups in advanced stages of atrophy. In five trial periods in two cases we observed that when the administration of cytochrome C was interrupted, disability increased after a period of from three to five days, but improvement was again apparent in from two to three days after the administration of the material was resumed.

It is of interest that in one patient with severe disability resulting from multiple sclerosis, muscular stiffness and weakness were similarly improved. In one patient with chronic anterior poliomyelitis, improvement in muscular strength was moderate, and in two patients with acute anterior poliomyelitis, decrease in muscle spasm and pain was only suggestive. In two patients with myotonia atrophica, cytochrome C was without effect on the myotonia or muscular weakness.

At the present time, the observations are too incomplete to hypothesize on the mechanism of the action of the cytochrome C in these conditions or to predict the value of this preparation in the management of patients over long periods of time.

PROGRESSIVE MUSCULAR DYSTROPHY

This is characterized by progressive muscular wasting and weakness of the muscles,

often associated with an infiltration and overgrowth of fat (pseudohypertrophy) and a tendency to the development of muscular contractures. While several different forms are recognized, the condition may be considered as a clinical and pathological unit in which the various types cannot be distinguished by any fundamental differences.

The condition resembles in its essentials the muscular dystrophy experimentally induced in animals by dietary deprivation of vitamin E, or by measures that either destroy the vitamin in the intestinal tract or prevent its absorption. For example, the ingestion of large amounts of unsaturated fats may destroy the vitamin, or a biliary fistula with consequent lack of bile may prevent absorption of vitamin E. In the muscular dystrophy of the laboratory, the oral administration of vitamin E is followed by a rapid diminution in creatinuria and a rapid improvement in muscular function and structure. The vitamin is ineffective when given parenterally. In patients with progressive muscular dystrophy, vitamin E is without effect regardless of the mode of administration. This does not necessarily imply that muscular dystrophy in man is not due to a deficiency of vitamin E. In fact, our observations suggest that progressive muscular dystrophy is due to a defect in the utilization of vitamin E, and that the site of this defect is in the gastrointestinal tract. Support for this opinion is furnished by the following observations which we have made during the past few years:

1. If a *normal* subject ingests a test dose of vitamin E, namely, 0.6 Gm. of synthetic alpha tocopherol, and about one-half hour later the gastric contents are aspirated and fed to a patient with dystrophy, there may follow a definite decrease in the creatinuria which appears in twenty-four to forty-eight hours and lasts a few days.

2. In patients with dystrophy, the daily administration of whole wheat germ in amounts of at least 125 Gm. may likewise decrease the creatinuria, but to a lesser degree than does the vitamin after incubation with normal gastric juice. This effect is reduced but not abolished if wheat germ is given which has been previously extracted with ethyl ether. Wheat germ extracted with ethylene dichloride is without effect, and the residue of the ethylene dichloride extraction contains active constituents which may reduce the creatinuria.

3. Microscopic examination of wheat germ after ethyl ether extraction shows that the pectin portion still contains oily material that is readily removed by ethylene dichloride. Further investigation of all the known constituents of pectin showed that some of the sugars, namely, mannose, galactose or arabinose, were capable of increasing the utilization of vitamin E as indicated by a prompt reduction of excreted creatine and an increase in the output of preformed creatinine when the sugar was administered simultaneously with the vitamin. Inositol and propylene glycol have similar but less marked effects. These findings, therefore, indicate the existence of a group of "accessory substances" which are important in the utilization of vitamin E.

4. Observations in one of our patients suggest that the onset of muscular dystrophy during puberty or even later in life may be influenced by a lack of lactase, the enzyme which is normally present in the intestinal tract and hydrolyzes lactose to equal quantities of galactose and glucose. Although galactose itself was active as an "accessory substance," lactose which normally supplies galactose in this case was without influence on the creatine output. This was the only patient in whom the accessory action of lactose had been studied. On the other hand, raffinose, a trisaccharide that contains galactose and is hydrolyzed by alpha-galactosidase, an enzyme different from lactase, proved active. In fact, galactose given as

raffinose, appeared to have even more effect than galactose itself.

If these sugars and sugar alcohols are necessary for the utilization of vitamin E, the question arises as to whether they are present in the normal gastrointestinal tract. The question is pertinent since vitamin E is effective in animals with experimental muscular dystrophy even if given without food. Gastric mucin promised to be a likely source of accessory substances since its polysaccharide portion is similar to pectin. As we anticipated, we found that in certain patients with dystrophy, gastric mucin is apparently split in the intestinal tract to furnish substances that promote the utilization of vitamin E. We found that when the vitamin was given either with gastric mucin, or with l-fucose, a sugar present in mucin, the creatine output was promptly reduced. Moreover, both galactose and mannose are present in gastric mucin.

The exact nature of the defect responsible for progressive muscular dystrophy in man is not yet established, but the evidence at hand suggests that a lack of these so-called "accessory substances" or a disturbance of the enzyme system involved in their reactions with vitamin E may play an important rôle.

A few patients in whom the downhill course of the disease is relatively slow, have shown clinical improvement when combinations of vitamin E and the "accessory substances" in the form of sugars or mucin are fed to them. On the other hand, no clinical effects have been noted in the majority of patients. It is probable that greater therapeutic effects will result from more efficient preparations of the "accessory substances" or some product of their reaction with vitamin E.

General measures offer little in the treatment of progressive muscular dystrophy. Since prolonged physical inactivity induces more rapid progression of disability and brings about earlier development of contractures, undue restriction of activity is contraindicated. Physical therapy does not affect the underlying pathological process, but it does help maintain muscular function and prevent contractures and is of real importance in the management of these patients.

Numerous other measures have been employed, including a long list of vitamins and endocrine preparations, which have been without significant effect on the course of the disease.

HYPERTHYROIDISM

Occasionally the muscular changes of Graves' disease simulate those of myasthenia gravis, progressive muscular dystrophy or progressive muscular atrophy or increase the disability of these conditions when they are associated. In many of these cases the diagnosis of Graves' disease may be obvious and may suggest the method of treatment, but in others the signs of thyroid dysfunction may be obscure. However, it is known that the muscular changes of Graves' disease are associated with a gross creatinuria which may be abolished by the administration of iodine, whereas the creatinuria of progressive muscular dystrophy appears not to be influenced by the administration of iodine. Furthermore, in muscular dystrophy, although usually not in Graves' disease, the creatinuria is associated with an appreciable reduction in the urinary output of preformed creatinine. These differences are helpful in determining the etiology of the defect in creatine metabolism. Myasthenia gravis is not associated with a significant creatinuria except in those patients whose course is progressing rapidly to a fatal outcome or in those in the advanced stages of chronic disease.

Obviously, when muscular dysfunction is induced or increased by concomitant Graves'

disease, the management must include treatment of the hyperthyroidism.

DR. GOLD: The subject is now open for discussion. Are there any questions?

DR. EPHRAIM SHORR: May I ask, Dr. Milhorat, whether there is any difference in the clinical response to neostigmine in Graves' disease and in myasthenia gravis which might serve as a means of differential diagnosis?

DR. MILHORAT: I think that each of these conditions is likely to respond to neostigmine. The evidence on that point is not clear however, because frequently we do not know whether we are dealing with a myasthenic picture produced by Graves' disease, or with a mild form of myasthenia gravis associated with Graves' disease. I should like to hear what you think about it.

DR. SHORR: In a recent study, Thorn and Eder state that they regard a favorable response to neostigmine as diagnostic of true myasthenia gravis, so that whenever such a favorable response is obtained in a patient with Graves' disease, they infer that the two conditions coexist. However, what Dr. Milhorat says about the failure of neostigmine to differentiate between true myasthenia gravis and a similar clinical picture due to Graves' disease indicates that the differential diagnosis between these two conditions is frequently difficult and sometimes impossible. Problems of this character are met with frequently and indeed, one confronts us on the wards of the hospital at this time. The patient gives a history typical of Graves' disease complicated by a severe exophthalmos. Following a thyroidectomy the patient returned to the hospital with the marked muscular weakness characteristic of myasthenia gravis and an appreciable creatinuria. This patient responds to neostigmine regularly and undoubtedly specifically, as shown by the absence of any effect of placebos. However, in myasthenia gravis we ordinarily expect no creatinuria of any significant degree except when the condition is profound and generalized and the patient critically ill. We would therefore assume that the creatinuria is due to the thyroid dysfunction and would expect it to be abolished by iodine.

This abolition of the creatinuria of Graves' disease by iodine is generally used to differentiate the myasthenias and myopathies of Graves' disease from true myopathies, such as progressive muscular dystrophy. It is frequently impossible to differentiate these conditions on clinical grounds alone, because the myopathies of Graves' disease simulate very closely those seen in typical progressive muscular dystrophy.

In 1932, studies which I carried out in collaboration with Drs. Richardson and Wolff indicated that the creatinuria of progressive muscular dystrophy is unaffected by iodine. Since then we have had a number of cases of Graves' disease with muscular wasting, sometimes generalized and sometimes confined to the shoulder girdle, and we have relied upon the use of iodine to differentiate these conditions. However, we have since become a little less certain about the universal application of this rule. Seven or eight years ago we studied such a patient in whom severe wasting of the muscles of the shoulder girdle was associated with typical Graves' disease and a marked creatinuria which was completely abolished by the administration of iodine. Following thyroidectomy her Graves' disease subsided and there was a marked improvement in the muscle mass and function. Within the past two years however, this patient, who has remained free of all signs and symptoms of Graves' disease, has developed a progressive spontaneous creatinuria. In this same interval, a brother in his twenties developed typical signs of progressive muscular dystrophy with no evidence whatsoever of Graves' disease.

DR. GOLD: Does she not have both dis-

eases, first Graves' disease and now progressive muscular dystrophy?

DR. SHORR: It is a possibility which must be considered. Her brother, who has typical symptoms of progressive muscular dystrophy, in a recent creatine tolerance test was found to have no spontaneous creatinuria. Apparently then, we may encounter an occasional case of progressive muscular dystrophy in young adults in their twenties, without creatinuria or impairment of creatine tolerance.

DR. MILHORAT: The absence of creatinuria in muscular dystrophy of late onset, for instance in the twenties, is not unusual. While muscular dystrophy is essentially a disease of early childhood, many patients have an onset at puberty. In these cases, muscular wasting is often confined for many years to limited groups of muscles, and creatinuria is either minimal or absent. Ultimately, when the muscular wasting becomes widespread, creatinuria appears and progressively increases. The course in these patients with a negligible degree of creatinuria is usually slow.

DR. SHORR: Certainly the occasional absence of creatinuria in progressive muscular dystrophy reduces the confidence with which we can apply the iodine sensitivity test in the differential diagnosis of this condition. For the most part, however, our own studies, as well as those in the literature, suggest that most instances of such muscle wasting in Graves' disease represent a manifestation of the *one* disease, and may be expected to be corrected by the proper management of the Graves' disease.

DR. MILHORAT: I am not entirely in agreement with Dr. Shorr's point of view. While we all recognize the frequency with which creatinuria and muscular weakness occur in Graves' disease, I believe that all, or nearly all, of the reported instances in which Graves' disease simulates progressive muscular dystrophy, or progressive spinal muscular atrophy, represent the association of two diseases.

DR. JANET TRAVELL: When a creatinuria is present in myasthenis gravis, is the excretion of creatine influenced by neostigmine? If so, it might help in the differential diagnosis.

DR. MILHORAT: No, neostigmine has no effect on the creatinuria of myasthenia gravis when this is present.

DR. TRAVELL: I should like to ask whether there are any other conditions of disorders of the muscles besides progressive muscular dystrophy and Graves' disease, and perhaps myasthenia gravis, which show a spontaneous creatinuria?

DR. MILHORAT: Spontaneous creatinuria may occur in any process that results in wasting of most of the muscles of the body. An outstanding example of this is dermatomyositis. In that condition the muscular wasting can be as extensive as that seen in the advanced stages of muscular dystrophy, and the creatinuria is likewise of the same order as in muscular dystrophy.

DR. TRAVELL: With impaired retention of ingested creatine?

DR. MILHORAT: Yes. The impairment in retention of creatine may be so gross that all of an ingested test dose will be excreted in the urine.

DR. TRAVELL: Do these cases respond to vitamin E?

DR. MILHORAT: They do not respond to vitamin E given alone.

DR. TRAVELL: What are the normal values for the twenty-four-hour excretion of creatine in the urine and for the retention of ingested creatine?

DR. MILHORAT: The normal adult male excretes either no creatine at all or only negligible amounts, that is, up to 42 mg., and is able to retain all or practically all of an oral test dose of from 1 to 2 Gm. of creatine. Women often excrete up to 60 mg. of creatine daily and the retention of in-

gested creatine is somewhat lower than in men; a retention of 75 per cent or more of the test dose is usually considered normal. Infants and children normally excrete appreciable amounts of creatine depending on their age, and they retain less ingested creatine than adults.

DR. GOLD: Dr. Shorr, do your values for the normal agree with these figures?

DR. SHORR: Yes. We take about 50 mg. of creatine in twenty-four hours as the upper limit of the normal excretion on a creatine-free diet, but minor increases above this amount are not considered significant. Men usually excrete slightly less than 50 mg. We find that normal individuals when given a test dose of 1.32 Gm. of creatine, usually retain at least 70 per cent of the dose; men on the average, retain somewhat more than women.

DR. TRAVELL: How does the ingestion of protein influence the urinary excretion of creatine?

DR. MILHORAT: Large amounts of protein may increase the excretion of creatine, since the substances from which the body builds creatine are the amino acids, glycine and arginine. The methyl group of creatine can be furnished either by the amino acid methionine or by choline.

DR. TRAVELL: In studying creatine metabolism, it is important then, to put the subject on a "creatine-free" diet, which contains no meat or fish products, during the period of urine collection

DR. MILHORAT: Yes. About 95 per cent of the creatine in the body is found in the muscles, and since meat and fish products are usually derived from muscle tissue, diets not free from these foodstuffs will contain large and undetermined amounts of creatine. When meat or fish are eaten, one cannot tell how much of the excreted creatine is lost from the patient's muscles and how much is derived from food.

DR. TRAVELL: From how much protein is 1.32 Gm. of creatine derived? That is the amount used in the standard creatine tolerance test.

DR. MILHORAT: Ox muscle contains about 400 mg. of creatine per 100 Gm. of muscle. Therefore, 1.32 Gm. of creatine represents about three-quarters of a pound of meat. Vegetable protein does not contain creatine but is rich in the materials from which creatine is made in the body.

DR. TRAVELL: You spoke of changes in the output of creatinine as being of diagnostic significance in progressive muscular dystrophy. Would you tell us what are the normal values for the excretion of this material and its relation to the creatine output?

DR. MILHORAT: The muscles convert creatine into creatinine which is then promptly excreted in the urine. The amount of creatinine in the urine has a definite relationship to the total mass of the body. Thus, men with large, well developed muscles, as a rule, excrete more creatinine than do women, and adults, more than children. The normal man excretes about 25 mg. of creatinine per Kg. of body weight per day and the normal woman about 15 to 20 mg. This amount is reduced in muscular dystrophy in proportion to the degree of muscular wasting and may be as low as 3 to 5 mg.

DR. TRAVELL: We have a group of patients, both men and women, who show a spontaneous creatinuria and impaired retention of creatine and who do not exactly fit into any of the categories described by Dr. Milhorat. These are physically active persons without visible muscular wasting and whose major complaint is a chronic pain apparently of a muscular origin. They have recurrent attacks of severe and at times incapacitating pain which is associated with spasm and tenderness of the muscles. As a rule, physical examination is otherwise negative, and all sorts of laboratory tests except the creatine tolerance test are also

normal. Dr. Shorr has been interested in these patients. The usual diagnosis in such cases has been chronic fibromyositis, although we prefer the term chronic myalgia or fibromyalgia, which is clinically more descriptive since evidences of infection are usually lacking. Brochner-Mortensen in 1941 reported in the *Acta medica Scandinavica* that he found a significant creatinuria in a similar group of twenty men with myalgia, or myosis, as he called it. I should like to ask Dr. Milhorat whether he has observed any such cases?

DR. MILHORAT: I have seen similar patients with these muscular symptoms and creatinuria.

DR. TRAVELL: Does the creatinuria in these cases respond to vitamin E when given together with the factors which increase its utilization?

DR. MILHORAT: No, we have not detected any such response.

DR. TRAVELL: Then, would you say that this type of disorder is not related to dermatomyositis?

DR. MILHORAT: The condition appears to be different from dermatomyositis in many respects.

DR. TRAVELL: In view of your finding that certain "accessory factors" are necessary for the utilization of vitamin E in progressive muscular dystrophy and dermatomyositis, as indicated by changes in the urinary excretion of creatine, would you say that these conditions represent nutritional deficiencies?

DR. MILHORAT: In my opinion, progressive muscular dystrophy probably has such an etiology. It is not due to a dietary deficiency but rather to a utilization defect possibly something like that seen in pernicious anemia. We do not have enough data on which to make a statement for the remainder of these muscular diseases.

DR. MAYNARD B. CHENOWETH: Dr. Milhorat, can you give us any information about di-isopropyl-fluorophosphate in the treatment of myasthenia gravis?

DR. MILHORAT: Such limited observations as I have made suggest that this agent offers no advantage over neostigmine and probably will not find a prominent place in the management of myasthenia gravis.

DR. MCKEEN CATTELL: Dr. Riker has made some observations which bear on Dr. Chenoweth's question.

DR. WALTER RIKER: The rationale for the use of di-isopropyl-fluorophosphate, or DFP for short, in this condition was based on the fact that this agent is a potent inactivator of cholinesterase. In contrast to neostigmine or physostigmine, DFP effects an irreversible inactivation of cholinesterase, as demonstrated by Mazur and Bodansky. Dr. Clarke Wescoe and I administered DFP to patients suffering from myasthenia gravis. The doses employed were increased gradually in order to decrease the cholinesterase activity of red blood cells to levels approximating 20 to 30 per cent of normal. These patients did not manifest any definite improvement in response to DFP therapy. We were of the opinion that the response to neostigmine was somewhat better after the DFP, but we were unable to evaluate this with any degree of certainty.

We were struck by the fact that doses of neostigmine, of the order of 0.5 to 1.0 mg. given parenterally, had virtually no effect on red blood cell cholinesterase, and yet produced the characteristic amelioration of symptoms. We investigated the actions of DFP and neostigmine in the experimental animal. We found that the intra-arterial injection of DFP alone produced a series of fasciculations after a latency of one to five minutes. Neostigmine alone, injected arterially, produced an immediate contraction of the muscle followed by a series of weaker and repetitive contractile responses. This also occurred when neostigmine was similarly injected after the intra-arterial injection

of DFP and at a time when the cholinesterase of the muscle was found to be completely inactivated. This action of neostigmine in the absence of cholinesterase was further substantiated in chronically denervated muscle in which an immediate acetylcholine-like contracture was produced by the intra-arterial injection of this agent. In contrast to this, DFP was entirely without effect. We concluded that neostigmine, among other actions, exerts a direct action on striated muscle, and that its therapeutic value in myasthenia gravis is due to this direct action which is similar to that of acetylcholine.

DR. CHENOWETH: Would you and Dr. Milhorat agree that the efficacy of neostigmine in myasthenia gravis is due to its direct action on the muscle?

DR. MILHORAT: No, I would not. It is possible that all the therapeutic effects of neostigmine and physostigmine are due to a direct action on the muscle, but the clinical evidence is not sufficient to warrant such a statement.

DR. GOLD: Dr. Milhorat, you said that if a patient with myasthenia gravis continues to receive neostigmine there is a tendency for the development of tolerance so that the patient requires increasing amounts of the drug to secure the same effect, and that if the doses are excessive, aside from toxic symptoms relating to other structures, the muscular weakness may actually increase. Why does the muscular weakness increase? How do you view the development of tolerance?

DR. MILHORAT: I think that the increasing need of the patient does not represent the development of true tolerance but rather the development of a relatively refractory state of the muscle. It is probably due to the fact that the patient is worse than he was before. I am speaking now of changes over a long period of time.

DR. GOLD: Do you mean that the disease has progressed or that a need for larger doses of the drug has developed because of its prolonged use?

DR. MILHORAT: The disease has progressed, and therefore greater stimulus is required for muscular contraction.

DR. GOLD: Now for the other question, what is the mechanism by which excessive doses of neostigmine make the muscular condition worse?

DR. MILHORAT: As I have said, when very large doses of neostigmine are given, within a matter of a few hours or a day there follows a period during which increased doses of the drug must be given. It can be demonstrated at this time that doses of neostigmine which previously had induced a favorable change, will now produce a far smaller change. Why that is, I do not know.

DR. GOLD: That does not quite explain why large doses make the patient worse.

DR. RIKER: It is well known that an excessive accumulation of acetylcholine at the neuromuscular junction results in a refractory state of the muscle. In the experimental animal, when the cholinesterase in the muscle is inactivated by di-isopropyl fluorophosphate, the subsequent injection of acetylcholine leads to a refractory state of the muscle so that it is unresponsive to both acetylcholine and nerve stimulation. A similar effect is observed when neostigmine is used instead of acetylcholine. As Dr. Milhorat has mentioned, excessive doses of neostigmine to patients with myasthenia gravis usually result in an increased degree of muscular weakness. In this and other respects, neostigmine behaves like acetylcholine. I think it should be stressed that in the management of myasthenia gravis, the dose of neostigmine should be strictly limited. Certainly it is the only really effective agent available. Since large doses may be harmful, the aim in treatment should not be to restore complete function, but only to effect some improvement and

thus avoid the risk of producing a refractory state in the muscle.

DR. GOLD: I wonder if we could have a word on the possible use of DFP in myotonia congenita?

DR. CATTELL: It might sensitize to the curare-like action of acetylcholine in the muscle, but since DFP reduces cholinesterase this latter action might make the myotonia worse because of the resulting increase in acetylcholine.

DR. GOLD: I was wondering about producing the curare-like action of DFP while blocking the cholinergic action of DFP by means of atropine.

DR. CATTELL: DFP does not have a direct curare-like action. The curare-like effect appears only because DFP allows the accumulation of acetylcholine.

DR. GOLD: I was referring to the observations in cats, namely, that large doses of DFP produce cholinergic effects which can be counteracted by atropine, and also muscular weakness and fatigue that is not overcome by atropine. I believe that the latter action sometimes lasted for months after the dose and in some cases seemed permanent. These animals sometimes behaved like patients with myasthenia gravis. Such an action might possibly be of value in myotonia congenita.

DR. CHENOWETH: In regard to the action of curare in myotonia congenita, there is an experimental condition resembling myotonia in which a drug, namely, 2,4 dichlorophenoxy acetic acid, or 2,4 D for short, produces in rabbits an inability of the muscles to relax; it is associated with fine fasciculation of the muscle fibers. The analogy extends further, in that the symptoms can be completely abolished by quinine and partially relieved by calcium. However, curare in any dose, given as intocostrin, does not influence the condition.

DR. MILHORAT: The answer is that these have never been tried.

DR. CATTELL: In line with that, curare is now being used clinically in various muscular disorders. Has that been tested in any of the diseases which you have mentioned?

DR. MILHORAT: It has been tried in various spastic states of a muscle, but I know of no instance in which curare has been used for the treatment of myotonia.

DR. CATTELL: It would be desirable to know the answer. Most of us assume that the effect of quinine is related to its curare-like action.

DR. SEYMOUR H. RINZLER: Would Dr. Milhorat explain the efficacy of neostigmine in such widely different conditions as myasthenia gravis, in which there is flaccidity of the muscles, and those disorders which are characterized by spasticity of the muscles, for instance the spastic paralysis following cerebral thrombosis or acute anterior poliomyelitis. There are numerous reports of the successful use of neostigmine in such spastic states.

DR. MILHORAT: I know that much has been said about its usefulness in patients with spastic conditions, but I have never seen any beneficial effect of neostigmine in decreasing spastic states of muscles. In fact, certain types of muscular rigidity, for example that of Parkinson's disease, are increased by neostigmine.

DR. GOLD: Dr. Milhorat, would you say something about aminoacetic acid, or glycine? We used to hear a lot about that in the treatment of muscular dystrophy.

DR. MILHORAT: Aminoacetic acid was employed for some time, but it is no longer used to any great extent in the management of patients with progressive muscular dystrophy or myasthenia gravis. It appears to be of some value in myasthenia gravis, but the effect of glycine is so small when compared to that of neostigmine, that we find it unprofitable to use. In progressive muscular dystrophy, glycine is without effect in

most instances. However, in those forms in which the symptoms appear late, namely, in the Landouzy-Dejerine type, aminoacetic acid is sometimes of value in decreasing muscular fatigue, although it apparently has no effect on the underlying dystrophic process.

DR. WALTER MODELL: Years ago ephedrine and amytal were popular in the treatment of myasthenia gravis. What has happened to them?

DR. MILHORAT: Ephedrine sulphate given in doses of about 7 mg. three times a day by mouth, frequently is of value in myasthenia gravis, but so many patients complain of the side effects, such as headache and tachycardia, that the usefulness of that drug is limited. Patients who require increasing doses of prostigmine usually are given at least a trial of ephedrine, and in certain instances it is a valuable adjunct.

DR. MODELL: You use it without amytal? Once it was combined or mixed with it.

DR. MILHORAT: In my experience, amytal is contraindicated. Many patients with myasthenia gravis complain of increased weakness following the use of sedatives.

DR. GOLD: There is a nice pharmacological observation in your application of neostigmine. You stated that the peak effect after intramuscular injection is reached within less than half an hour, after which the effects begin to wear off and in about three hours have largely disappeared. The patient with myasthenia gravis provides us with the curve of action of neostigmine, because there are fairly sharp end-points to mark the beginning and end of the effect. Neostigmine is often used for intestinal distention in a dose given once every six hours or so. It is clear from Dr. Milhorat's observations that, if the first dose does not accomplish the result, the second dose repeated six hours later will not do anything either, because under those conditions, there is no cumulation of the drug. This has nothing to do directly with muscle diseases, but here there is the opportunity to make an important type of pharmacological observation. Are there any more questions?

DR. MILHORAT: May I just make one historical comment?

DR. GOLD: Please do.

DR. MILHORAT: Sometimes we think that our concepts of physostigmine actions are of recent origin. In his article published in the *Klinische Wochenschrift*, January 7, 1895, Jolly described the myasthenic reaction with which his name is often associated. While the response of the muscles in myasthenia gravis appeared to be normal when faradic current was employed, definite fatigability was demonstrated with the use of a tetanizing current. After each succeeding stimulus, the response became less complete until finally the contractions ceased entirely. Jolly also pointed out that certain alkaloids, namely veratrine and physostigmine, may induce changes in the muscle that resemble those seen in myotonia congenita. Since the muscular state in myasthenia gravis appeared to be the opposite of that seen in myotonia congenita, Jolly suggested that pharmacological agents such as physostigmine, which induce a pharmacological effect opposite to that of the myasthenic reaction, should be sought for in the management of myasthenia gravis. Physostigmine was tried by Jolly, but the side-effects were so pronounced that he thought the use of the drug would have to be restricted to patients under observation in a hospital.

SUMMARY

DR. TRAVELL: The list of chronic diseases of the skeletal muscles which we have considered today includes myasthenia gravis, myotonia congenita, myotonia atrophica, familial periodic paralysis, amyotrophic lateral sclerosis, progressive muscular atro-

phy, progressive muscular dystrophy, the myopathies of Graves' disease, dermatomyositis and fibromyositis (fibromyalgia).

These conditions are distinguished from each other by a variety of clinical features and their differential diagnosis is not ordinarily difficult. However myasthenic symptoms may sometimes complicate the picture of Graves' disease and raise the question of the coexistence of a primary muscular dystrophy and hyperthyroidism. The fact that iodine administration in Graves' disease reduces the spontaneous creatinuria and increases the retention of creatine often serves to differentiate the two. Neostigmine relieves the myasthenic symptoms in both conditions and does not influence creatine excretion in either. In view of the diagnostic, and at times prognostic value of the creatine tolerance test, the normal values and standard conditions for this test are discussed.

The causes of the chronic muscular diseases listed above are unknown and their treatment is, for the most part, unsatisfactory. The drugs and measures which received special consideration are neostigmine, thymectomy, quinine, ephedrine, epinephrine, calcium, potassium chloride, cytochrome C, vitamin E with accessory factors and glycine.

In myasthenia gravis, removal of the thymus appears to cure a small proportion of cases. Neostigmine is highly effective in relieving the muscular weakness and fatigue. It is a double-edged sword and proper dosage is a matter of the greatest importance. There was a belief that the therapeutic effect resulted from its inhibition of cholinesterase, but now there is new evidence indicating that the beneficial effect is due to direct stimulation of the muscle, and that excessive doses may increase the weakness through the anticholinesterase action which gives rise to a curare-like effect of the increased acetylcholine at the muscle.

In familial periodic paralysis, an oral dose of 5 Gm. of potassium chloride often relieves the attack promptly, and doses of 2 to 4 Gm. daily may prevent recurrences.

In myotonia congenita, quinine, in oral doses of from 0.3 to 0.6 Gm. several times daily, often accelerates the muscular relaxation after a movement. Epinephrine and calcium are also sometimes of value.

There are preliminary observations indicating that daily intravenous doses of 50 mg. of cytochrome C may control the muscular disability of amyotrophic lateral sclerosis and related diseases.

New observations suggest that in progressive muscular dystrophy and dermatomyositis certain "accessory substances" are needed for the utilization of vitamin E, as indicated by diminished urinary excretion of creatine, following their administration. Preparations which when fed together with vitamin E to patients with these disorders have been shown to have an effect on creatine excretion, include normal gastric juice, certain sugars present in pectin and wheat germ, and also gastric mucin which contains some of the polysaccharides shown to act as "accessory substances." The clinical importance of these dietary factors has not as yet been satisfactorily demonstrated. The results open up the vista, however, that the etiology of these, and possibly of other members of this group of diseases, may be specific nutritional defects, and point the way to new lines of investigation for the solution of the vexing problems of therapy in these progressive muscular diseases.

Clinico-pathological Conference

Hemiplegia Due to Intracranial Mass*

STENOGRAPHIC reports, edited by Robert J. Glaser, M.D., of weekly clinico-pathological conferences, held in the Barnes Hospital are published in each issue of the Journal. These conferences are participated in jointly by members of the Departments of Internal Medicine and Pathology of the Washington University School of Medicine and by Junior and Senior medical students.

THE patient was a sixty year old white, retired railroad employee who entered the Barnes Hospital on April 23, 1946, complaining of paralysis of the left arm and left leg. The family history was of interest in that the patient's mother had died of diabetes at the age of sixty-nine. The patient had enjoyed excellent health for most of his life. In childhood he had had several bouts of an illness described as malaria. At the age of forty-two he injured his leg and an infection developed which subsequently involved the bone. Following an operation there was complete recovery. The patient had been told that he had a large perforation of the nasal septum; he had never had an operation or injury involving the nose and was unaware of the origin of the perforation. Two years before admission he developed a hacking cough which was productive of thick, white sputum but never of blood. *X*-rays of his chest taken shortly after the onset of the cough were said to have shown "healed scars." One year prior to entry the patient stopped work because of increasing fatigue and eight months before admission he developed shortness of breath on exertion. For years he had consumed six drinks of whisky daily. In the year before entry he had lost no weight.

Nine days before admission, while walking, the patient noticed that his left foot seemed to swing out with each step; concomitantly his left arm felt "half asleep." Within a few minutes these complaints cleared completely and the patient was symptom-free until twenty-four hours later when he began to have jerking movements of the left leg and a sensation of tightness in the muscles of the left leg and arm. After several minutes the jerking movements stopped but from then on the patient was aware of a marked limitation in the use of both the left arm and leg. However, he was still able to walk without assistance. He was seen by a physician who told him that his blood pressure was "90." The patient was not dizzy, disoriented or weak. He slept well that night but on the following morning had paresthesias of the left arm and leg. Subsequently, the left arm and leg became progressively weaker and finally totally paralyzed. Aside from an occasional slight frontal headache the patient had had no other symptoms.

At the time of entry physical examination revealed the temperature to be 37°C., pulse 70, respirations 26 and blood pressure 130/80. The patient was a well nourished and well developed male who appeared comfortable and not ill. His complexion was florid. He coughed frequently during the examination and during the periods of coughing he became cyanotic. Aside from an ecchymosis over the left iliac crest the skin appeared normal. The pupils were equal and reacted well to light and accommodation. Examination of the fundi re-

* From the Departments of Internal Medicine and Pathology, Washington University School of Medicine and the Barnes Hospital, St. Louis, Mo.

vealed the discs and vessels to be normal; no hemorrhages or exudates were seen. The nasal septum was deviated to the right; a perforation, 1 cm. in diameter, was noted. The teeth were absent. The pharynx was moderately injected. The trachea was in the midline. On percussion the chest was hyperresonant throughout; the breath sounds were somewhat distant. Scattered moist râles and a few rhonchi were heard at the right base and in the right axilla. The heart was not enlarged and the sounds were rather distant; the second aortic sound was louder than the second pulmonic sound. The rhythm was regular and there were no murmurs. Examination of the abdomen revealed it to be soft; no organs or masses were palpable. The prostate was small. A well healed scar was noted over the left tibia. Neurologic examination revealed generalized constriction of the visual fields and slight ptosis of the left eyelid. There was no speech abnormality. The tongue deviated slightly to the right. The muscles on the left side of the neck were weak; the left trapezius was atrophied as was the left deltoid group. There was complete paralysis of the left arm and leg. No fibrillary twitchings were seen. Sensory examination was entirely normal. The left biceps and knee jerk were hyperactive; the toe signs were not pathologic.

The laboratory studies were as follows: Blood count: red cells, 4,640,000; hemoglobin, 14 Gm.; white cells, 6,400; differential count: stab forms, 10 per cent; segmented forms, 60 per cent; lymphocytes, 24 per cent; monocytes, 6 per cent. Urinalysis: negative. Stool: guaiac negative. Blood Kahn reaction: negative. Blood chemistry: non-protein nitrogen, 19 mg. per cent; total protein, 5.9 Gm. per cent; albumin, 3.5 Gm. per cent; globulin, 2.4 Gm. per cent; sugar, 73 mg. per cent; cephalin-cholesterol flocculation test, negative. Icterus index: 3. Sputum examination: no acid-fast bacilli found. Prothrombin time: 75 per cent of normal. Bleeding time: three minutes, ten seconds. Clotting time: eight minutes, sixteen seconds. Lumbar puncture: initial pressure, 190 mm. of water; final pressure, 160 mm. of water; cells, 6 lymphocytes; protein, 134 mg. per cent; sugar, 67 mg. per cent; chlorides, 124 milli-equivalents/liter; colloidal gold curve, 2222221000; Wassermann, negative. Roentgenogram of the chest: "The heart is slightly enlarged. The hilar shadows are large and contain many round deposits of calcification. There are several emphysematous blebs in the apex of the right upper lobe. There is moderate scoliosis of the thoracic spine with convexity to the left." Stereoscopic views of the skull: indeterminate. Electrocardiogram: normal.

Shortly after admission several observers detected the liver edge at the right costal margin and the tip of the spleen was likewise felt. On three occasions the urine was positive for bile. Liver function tests were as follows: icterus index, 9; alkaline phosphatase, 11 Bodansky units; bromsulfalein test, 22 per cent retention in 30 minutes. Several days after admission new ecchymotic areas appeared on the paralyzed side. A Rumpel-Leede test was positive. The platelet count was 234,000. Five days after entry a second lumbar puncture was performed. On this occasion the initial pressure was 90 and the final pressure 70 mm. of water. There were 9 lymphocytes; the protein was 139 mg. per cent, the chlorides 124 milli-equivalents/liter, the colloidal gold curve 1111110000, and the Ayala index 6.6. An electroencephalogram revealed a focus of borderline slow activity in the right temporo-occipital region.

On repeated examination wheezes were heard over both lungs and other signs consistent with emphysema were recorded.

On the eleventh hospital day the patient had a clonic convulsion which began in the left arm and which was accompanied by mild twitching of the left thigh muscles.

The episode lasted twenty-five minutes but there was no spread. Subsequently, several similar but more severe attacks occurred. Shortly after the first one began the patient had a shaking chill and his temperature rose to 39.7°C. Physical examination at this time revealed only injection of the conjunctivae and many moist râles in the right axilla and at the right base. The white blood count was 11,250 with 15 per cent stab forms, 73 per cent segmented forms and 12 per cent lymphocytes. Another roentgenogram of the chest showed little change from the findings on the first film. A blood culture was sterile. The urine examination remained normal except for occasional traces of bile. The purpura persisted but no further blood abnormalities were detected. Two weeks after admission the patient complained of abdominal pain and was noted to have tenderness and moderate muscle spasm in the epigastrium. His temperature continued to spike to 39°C. frequently and his white cell count rose to 14,000. Oral cholecystography was done and the gall-bladder was not visualized. An *x*-ray diagnosis of a "pathologic" gallbladder was made. A flat film of the abdomen revealed no abnormalities except for hypertrophic osteoarthropathy of the lumbar spine. After three and one-half weeks on the neuromedical service the patient was transferred to the neurosurgical service where the following positive findings were recorded on examination. There was a complete left facial paralysis and definite weakness and atrophy of the left sternomastoid and trapezius muscles. The left arm and hand were completely paralyzed and there was atrophy of the deltoid, triceps, and biceps groups as well as of the thenar muscles of the left hand. The left triceps and biceps reflexes were hyperactive. The intercostal muscles on the left seemed weak and the abdominal reflexes were absent bilaterally. The left leg was entirely paralyzed and vibratory sensation was absent. The knee jerk was hyperactive and the Babinski sign questionably positive. The sensory examination again was normal. Ventriculograms were done and the *x*-ray films showed a shift of the pineal gland to the left. There appeared to be a circular defect compressing the posterior part of the body of the right ventricle. Following ventriculography the patient was taken to the operating room; on exploration a necrotic area was encountered at a depth of 3 cm. in the right parietal area. Adjacent to the area of necrosis there was a firm, well demarcated tumor about the size of a plum; this mass was excised. Postoperatively the patient did poorly and failed to regain motion in the left upper or lower extremities. He continued to have fever as high as 40.4°C. and his blood pressure fell to 98/68. He was placed in an oxygen tent and given whole blood transfusions and penicillin. A ventricular tap was performed but no evidence of increased intracranial pressure was found. Considerable respiratory difficulty required almost constant use of a suction apparatus. The patient responded enough to talk slightly but his respiratory difficulty persisted and shortly before death, Cheyne-Stokes breathing was noted. He failed rapidly and despite all supportive measures he died on May 26, 1946.

CLINICAL DISCUSSION

DR. HARRY L. ALEXANDER: This patient's illness was rather complicated. He had a chronic cough for several years, a palpable liver and spleen, *x*-ray evidence of a pathological condition of the gallbladder, signs suggesting mild liver insufficiency, and finally, neurologic signs suggestive of a brain tumor. Dr. Levy, from the data available, may the diagnosis of brain tumor be substantiated?

DR. IRWIN LEVY: That diagnosis was not obvious at the onset but there were clues which led one to suspect that a subcortical

brain tumor was present. Three factors in particular stand out; one, the progressive nature of the clinical symptomatology—particularly of the hemiparesis; two, the occurrence of convulsive seizures which are much more common with subcortical tumors than with vascular lesions; and three, the high spinal fluid protein on two different occasions.

DR. ALEXANDER: Do the ventriculograms confirm the diagnosis?

DR. LEVY: Yes, they definitely indicate a space-taking lesion.

DR. ALEXANDER: Apparently at the time of operation this tumor was well demarcated and easily excised. From this fact would you comment on the probable nature of the lesion?

DR. LEVY: Most subcortical tumors that can be shelled out without difficulty represent metastatic lesions.

DR. ALEXANDER: May the fever which was recorded during this patient's illness be explained on the basis of the brain lesion and particularly by the presence of areas of necrosis?

DR. LEVY: Acutely developing primary tumors may in themselves cause temperature elevation.

DR. ALEXANDER: This patient had a rather high degree of fever; frequent elevations to 39°C. were recorded.

DR. LEVY: Usually the fever associated with brain tumor is of a lesser magnitude.

DR. CARL G. HARFORD: In what portions of the brain is involvement by tumors most apt to produce fever?

DR. LEVY: One cannot be specific in answering that question. Various centers are recognized which are related to the vasomotor system. For example, area 6, the orbital surface of the frontal lobe, and certain areas in the hippocampus are thought to have autonomic function transmitting impulses to the hypothalamus and to the brain stem thus influencing body temperature. The hypothalamic centers which lie on either side of the optic chiasm may, when involved, give rise to hyperthermia or hypothermia. I have seen instances, when the posterior portion of the hypothalamus was involved, in which temperatures as low as 96°F. were persistently noted. As mentioned before, however, acutely developing tumors, regardless of their localization, are frequently associated with some temperature elevation.

DR. ALEXANDER: Would the amount of necrosis present in the tumor be related to the febrile response?

DR. LEVY: I do not think so for there is not good absorption from the brain.

DR. ALBERT ROOS: Dr. Levy, you stated that the lesion probably was located in the subcortical area. Does not the occurrence of convulsions suggest involvement of the cortex itself?

DR. LEVY: When the patient's presenting symptom is generalized convulsion, statistically a subcortical lesion is favored. When the cortex is involved, a Jacksonian march is more apt to occur.

DR. ALEXANDER: Dr. Levy has suggested that the tumor in the right parietal area was metastatic. If we consider this lesion to have been metastatic, where did the primary tumor arise? Frequently metastatic tumor of the brain is secondary to carcinoma of the lung. Dr. Goldman, do you believe the pulmonary signs and symptoms indicate that this patient had a lung tumor?

DR. ALFRED GOLDMAN: The prominent pulmonary symptoms in the history were cough, non-bloody sputum and dyspnea. Such symptoms plus the signs elicited in the physical examination suggest emphysema and bronchitis rather than a primary tumor. The *x*-ray findings were consistent with pneumonitis. However, as you have pointed out, Dr. Alexander, frequently metastatic tumors in the brain arise in the lung and bronchogenic carcinomas often are not

visible on *x*-ray. Sometimes the primary lesion is very small and if there is no bronchial obstruction, one is unable to identify the primary site.

DR. ALEXANDER: It is very important for us to determine, if this be a metastatic lesion, the primary site, and to discuss the mechanism by which the metastasis occurred. If the primary tumor was not in the lung, but rather in some other viscus, I would like to ask Dr. Robert Moore what the evidence is that tumor cells may pass through the lungs without giving rise to metastases there.

DR. ROBERT A. MOORE: Such a phenomenon has been postulated because of the fact that the pulmonary capillaries are slightly larger than the systemic capillaries. It has been suggested that individual tumor cells may pass through the lung to other sites. The recent evidence set forth by Batson regarding the vertebral veins as a pathway of metastases seems a much more logical explanation and has cast doubt on the previous hypothesis.

DR. ALEXANDER: This patient also had signs suggesting liver disease. Bile was found in the urine on several occasions. Would you discuss the liver function studies, Dr. Moore?

DR. CARL V. MOORE: This patient had a normal icteric index, a negative cephalin-cholesterol flocculation test, but an elevated alkaline phosphatase and definite bromsulfalein retention. These data suggest that there may have been localized lesions in the liver which may have accounted for the occasional presence of bile in the urine.

DR. ALEXANDER: Dr. Wade, do you believe the focal lesions were metastatic?

DR. LEO J. WADE: I believe this patient had obstructive jaundice but I am not sure that the obstruction was due to carcinoma. It is possible that there was a common duct stone which produced intermittent, low-grade obstruction.

DR. W. BARRY WOOD, JR.: Would not the abdominal pains likewise suggest intermittent obstruction?

FIG. 1. Carcinoma of the esophagus; photograph of gross specimen.

DR. ALEXANDER: There is considerable evidence to suggest gallbladder disease. The fever might have been due to common duct obstruction; if present, obstruction due to a stone bore no relation to the central nervous system lesion. Dr. Wade, may a focal lesion in the liver produce intermittent obstruction?

DR. WADE: I rather doubt that this occurs very often. Usually obstruction is not seen in metastatic disease unless there is invasion of the biliary tree and under such circumstances obstruction is usually complete.

DR. ALEXANDER: If you are considering the possibility of a tumor, would the fact that this patient had a definite alcoholic history influence your reasoning?

DR. WADE: I would be more concerned with his dietary history than with his alcoholic history. If the patient had adequate dietary habits, I do not believe that the amount of alcohol he consumed would have been significant.

DR. ALEXANDER: Dr. Reinhard, would you discuss the purpura which was noted in this case?

DR. EDWARD H. REINHARD: The data available do not indicate any abnormality in the clotting mechanism and one would therefore have to assume that the defect present involved the capillaries. I have no good explanation for possible increased

capillary permeability in this case. It is occasionally seen in carcinomatosis, but carcinomatosis seems unlikely here.

DR. ALEXANDER: It is of interest that the purpura was confined to the paralyzed side. Dr. Levy, have you seen this phenomenon before?

DR. LEVY: One notes vasomotor changes on the involved side in hemiparesis but I have not seen purpura before.

DR. WOOD: Is not edema the usual unilateral clinical manifestation in hemiplegia, Dr. Levy?

DR. LEVY: Yes.

DR. ALEXANDER: Are there any further suggestions?

DR. WOOD: It does not seem certain to me that this patient had a carcinoma. He gave no history of weight loss in the year preceding entrance to the hospital, and no evidence, either clinical or roentgenologic, was ever obtained of a tumor other than in the brain. The calcified hilar lymph nodes were prominent and suggest the possibility of either tuberculosis or histoplasmosis. I believe tuberculoma of the brain should be considered and I would like to know Dr. Goldman's opinion regarding the possibility of tuberculosis.

DR. GOLDMAN: Although I thought of tuberculoma as a possible explanation of the central nervous system lesion, the description at operation does not seem compatible. The appearance of the calcification in the hilar lymph nodes suggests the so-called "egg shell calcification" which is associated frequently with silico-tuberculosis.

DR. WOOD: Are lesions in the brain common in histoplasmosis?

DR. ROBERT J. GLASER: In the seventy-one cases described in the extensive review of Parsons and Zarafonetis,* involvement of the brain is recorded only once.

DR. WADE: There is a suggestion of superior vena cava obstruction, possibly from a mediastinal mass, for the patient is described as having had florid complexion and is said to have become cyanotic when he coughed.

DR. ALEXANDER: As has been pointed out, however, this man had many signs suggesting emphysema and in such a patient those changes may be observed.

DR. HARFORD: There appeared to be slight elevation of the right leaf of the diaphragm. Could this be considered evidence of a metastatic lesion in the liver?

DR. DONALD S. BOTTOM: The diaphragm on the right had a lobulated appearance which is seen not infrequently in normal patients; however, without a lateral view, it is not possible to rule out completely either a supradiaphragmatic or subdiaphragmatic lesion.

DR. ALEXANDER: In view of the emphysema would you not have expected the diaphragms to be lower?

DR. BOTTOM: Usually they are low in emphysema.

DR. ALEXANDER: In summary, it seems that the consensus of opinion of the staff favors a metastatic rather than a primary lesion in the brain. If the lesion be metastatic, the site of origin is not at all clear. The lungs seem to be an unlikely primary site and the evidence does not point to any other specific region. It is believed that the jaundice probably was due to intermittent obstruction of the common bile duct by a stone.

CLINICAL DIAGNOSIS: Metastatic carcinoma of the brain, primary site unknown.

PATHOLOGIC DISCUSSION

DR. FRANK A. TOWNSEND: At autopsy the primary tumor was found in the lower third of the esophagus. (Fig. 1.) It was a polypoid growth which partially filled the lumen; although it caused moderate dilatation,

* PARSONS, R. J. and ZARAFONETIS, C. J. D. Histoplasmosis in man. *Arch. Int. Med.*, 75: 1, 1945.

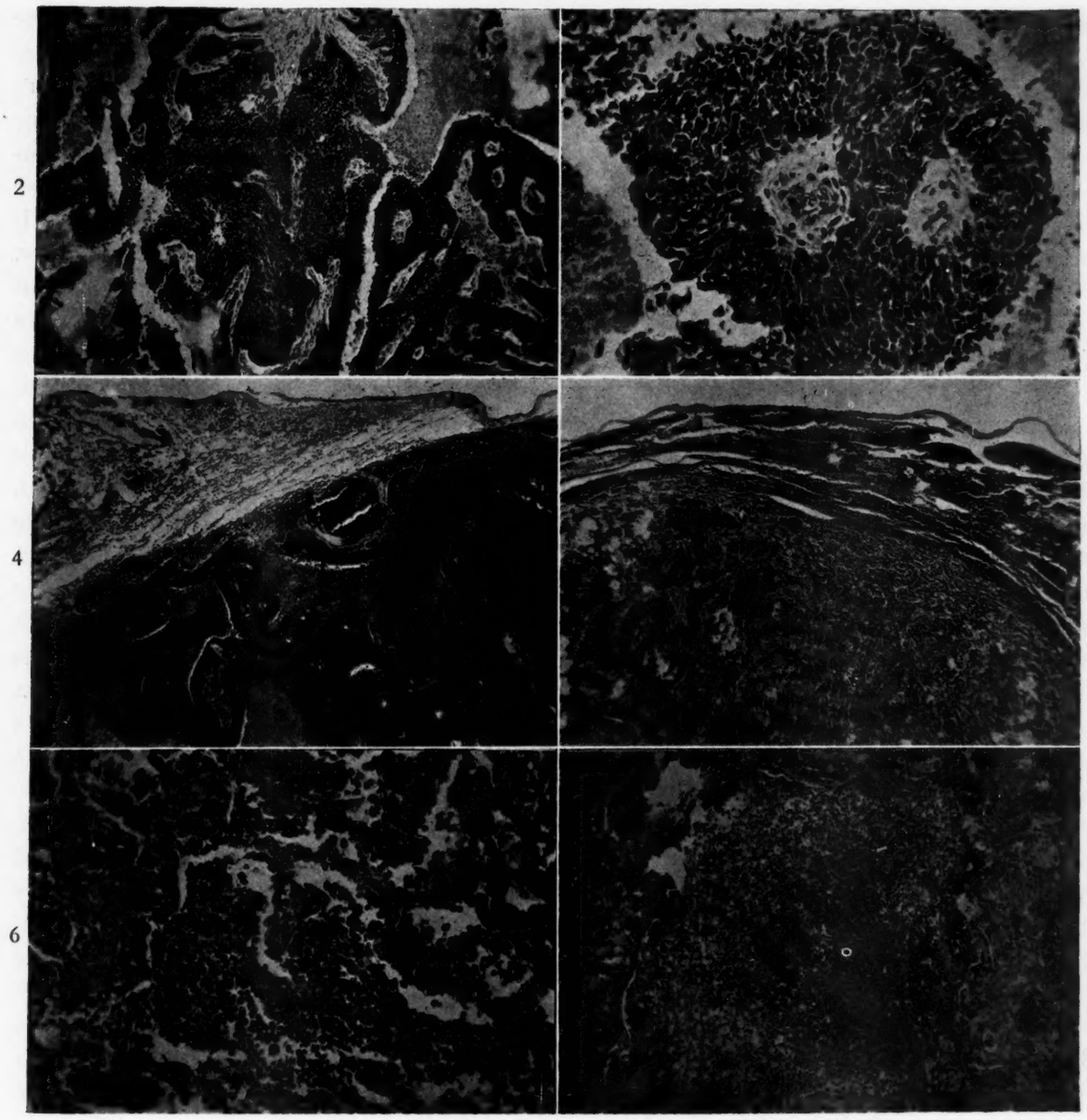

FIG. 2. Microscopic section of the esophageal tumor; note the absence of gland formation.
FIG. 3. High power view of the same section seen in Figure 2.
FIG. 4. Section of the metastatic nodule in the brain. Note the absence of tumor cells in the meninges.
FIG. 5. Section of the lymph node in the gastrohepatic omentum, showing carcinoma cells in the peripheral sinusoids.
FIG. 6. Section of the lung showing pneumonic exudate in the early stage of organization.
FIG. 7. Another section of the lung illustrating abscess formation. Note the infiltration by polymorphonuclear leukocytes.

there was no evidence of obstruction for the muscularis of the esophagus proximal to the tumor was not hypertrophied. In the right parietal region of the brain a tumor mass was found in the upper portion of the cerebral hemisphere just beneath the meninges. On cut section it appeared necrotic.

In addition, there were multiple abscesses in the lungs, measuring up to 2 cm. in diameter; these were associated with diffuse

FIG. 8. Section of a tracheobronchial lymph node illustrating one of the silicotic nodules.

bronchopneumonia involving all lobes of the lungs except the right middle lobe. The hilar lymph nodes were enlarged and firm and on section showed a marked degree of anthracosilicosis. There was advanced emphysema of the lungs. In addition, thrombi were present in the tertiary branches of the right pulmonary artery.

The liver was enlarged, weighing 1,850 Gm., and showed the changes of chronic passive congestion. The spleen, which was likewise enlarged, weighed 330 Gm. and contained much anthracotic pigment. Numerous small black stones, approximately 3 mm. in diameter, were found in the gallbladder but none were seen in the extrahepatic bile ducts. One node in the gastrohepatic omentum was large and firm. The cut surface bulged and was gray-white in color.

The heart was slightly enlarged weighing 420 Gm. The kidneys were normal in size but their surfaces were diffusely granular. These changes were interpreted as those of moderate arteriolar nephrosclerosis.

DR. R. A. MOORE: This patient had a primary carcinoma of the esophagus. The only demonstrable metastases were in the brain and in one lymph node of the gastrohepatic omentum. It was thus an unusual esophageal carcinoma in two respects. In the first place, there was no obstruction. The anatomic specimen confirmed the clinical history which contained no reference to the signs or symptoms of esophageal obstruction. Secondly, the metastases were unusual in their distribution. The presence of a metastatic lymph node in the gastrohepatic omentum is uncommon for the usual lymph drainage of the esophagus is into the posterior mediastinum. Further, solitary metastases in the brain, without evidence of metastases in other organs, is an unusual postmortem finding.

Evidence of malaria, either grossly or microscopically, was lacking. There was no increase in the reticulo-endothelial cells or in the amount of pigment in the spleen. In regard to the several episodes of jaundice noted during the patient's hospital stay, it can be said that the patient did have chronic cholecystitis and cholelithiasis. The calcium bilirubinate stones in the gallbladder suggest the possibility that on several occasions a stone had passed into the common bile duct and given rise to transient obstruction.

On section the hilar lymph nodes contained only a small amount of calcium, much less than would have been suggested by the degree of radio-opaqueness they exhibited on the *x*-ray film of the chest. Dr. Goldman suggested the possibility of silicosis and on the basis of the gross examination, it seems likely that silicotic pigment rather than calcium was responsible for the roentgenologic appearance of the nodes.

Turning to the microscopic sections, Figure 2 shows a characteristic section of the esophageal tumor. The cells are seen to be epithelial in type and show no glandular pattern, but foci of necrosis are present. The appearance is that of an epidermoid carcinoma, the type which constitutes approximately 90 per cent of the malignant tumors of the esophagus. A high power view of the same section (Fig. 3) confirms the diagnosis of epidermoid carcinoma. In the gross, the tumor was somewhat unusual for

it was almost entirely encapsulated. Most esophageal tumors of a comparable size undergo ulceration.

In Figure 4 a section of the cerebral metastasis is seen and shows the tumor to be of an identical cellular type. Although the metastatic nodule has extended to the meninges, no tumor cells are present in the meninges themselves. This type of tumor rarely disseminates diffusely through the subarachnoid space. Figure 5 is a section of the lymph node in the gastrohepatic omentum; in the peripheral sinusoids of the node the same cell type is again seen.

A section of the lung (Fig. 6) is illustrative of the characteristic exudate of a pneumonia in the early stage of organization. The proliferating fibroblasts are added evidence that the pneumonia has been present for some time. In Figure 7 there is liquefaction and abscess formation; the abscesses vary from 1 mm. to 2 cm. in diameter. The pulmonary epithelium is completely destroyed and is replaced by a fibrinous exudate which is infiltrated with polymorphonuclear leukocytes. The last section (Fig. 8) is a section of a tracheobronchial lymph node and shows the typical characteristics of a silicotic nodule.

DR. ALEXANDER: Do you believe that the proximity of the esophagus to the vertebral veins suggests that the cerebral metastases arose via that route?

DR. R. A. MOORE: That seems very likely but cannot be proven.

Final Anatomic Diagnosis: Epidermoid carcinoma of the esophagus with metastases to the brain and gastrohepatic lymph node; multiple abscesses of the lung; bronchopneumonia of the lung; thrombi of tertiary branches of the right pulmonary artery; arteriolar nephrosclerosis, moderate; anthracosilicosis of the lungs, tracheobronchial, bronchopulmonary, diaphragmatic, portahepatic, and retroperitoneal lymph nodes, and the spleen.

Western Society for Clinical Research

ORGANIZATION MEETING HELD IN SAN FRANCISCO, NOVEMBER 1 AND 2, 1946

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The purpose of this society is to foster clinical research in the West. The members of the new society, including representatives from Seattle, Salt Lake City, San Diego, Portland, San Francisco and Los Angeles, plan to pattern the organization and operation of the society in the tradition established by the Central Society for Clinical Research.

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ABSTRACTS

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Hyperplasia of the Gastric Mucosa in Man . . . . . ALVIN J. COX

Electrocardiographic Patterns of Ventricular Hypertrophy as Obtained by Unipolar Precordial and Limb Leads*

MAURICE SOKOLOW, M.D. *and* (*by invitation*) THOMAS P. LYON, M.D.

UNIPOLAR precordial and limb leads, with the use of Wilson's or Goldberger's central terminal, have clarified and extended our knowledge of electrocardiography. In the present study, the detailed patterns of right and left ventricular hypertrophy were determined by the use of unipolar leads and the findings correlated with the typical patterns obtained by the standard limb leads. One hundred cases of left ventricular hypertrophy and fifty cases of right ventricular hypertrophy were studied.

The pattern of left ventricular hypertrophy varied depending on the degree of hypertrophy and the presence of associated coronary disease. Not all the abnormalities characteristic of left ventricular hypertrophy were present in every case; in some cases only a single typical abnormality was present. The findings most commonly seen in left ventricular hypertrophy were (1) depression of the S-T intervals with a low, diphasic or inverted T wave in the left precordial leads; (2) a delayed onset of the intrinsic deflection (greater than 0.05 second) in the left precordial leads, especially V_5; (3) depression of the S-T interval with a low, diphasic or inverted T wave in lead aV_L in horizontal hearts (Wilson's criteria) and in lead aV_F in vertical hearts; (4) increased voltage R in left precordial leads and S in right precordial leads so as to present an R/S ratio smaller than normal in V_1 and an R/S ratio greater than normal in V_5.

The unipolar limb leads not infrequently were the only leads demonstrating significant abnormality. Lead aV_L frequently was more abnormal than lead I and on occasion presented abnormal ST-T changes when lead I was normal. In vertical hearts abnormal ST-T changes were noted on occasion in aV_F with normal or equivocal findings in leads II and III. In advanced cases, abnormal T waves were seen in aV_L, aV_F and aV_R with the last being characterized by an upright T wave. The ST-T changes, in general, were more frequent and more characteristic than was delayed onset of the intrinsic deflection. In many patients with left ventricular hypertrophy, confirmed by roentgenologic examination, left precordial leads did not show a delayed intrinsic deflection. On occasion, however, such delay was the only abnormal finding, and so of definite value.

Right ventricular hypertrophy was characterized by the following, not all of which need be present in every case: (1) a prominent, often tall R wave with an absent or minimal S wave in V_1 and/or V_2; (2) an abnormally great R/S ratio in V_1 and/or V_2; (3) a small R wave with a deep or prominent S wave in V_5 and/or V_6; (4) an abnormally small R/S ratio in V_5 and/or V_6; (5) delayed onset of the intrinsic deflection in V_1 (more than 0.03 second); (6) prominent R wave in lead aV_R; (7) depression of the S-T segment and inversion of the T waves in V_1 and/or V_2; (8) abnormal T waves in aV_L and/or aV_F, depending on the position of the heart.

The abnormalities seen in right ventricular hypertrophy are most typical in such diseases as tetralogy of Fallot. In chronic cor pulmonale associated with pulmonary fibrosis, emphysema, etc., the abnormalities are less marked and usually consist of small R waves and deep S waves with an abnormally small R/S ratio in V_5. The changes in V_1 are less frequently seen, in contrast with tetralogy of Fallot when V_1 is almost invariably abnormal.

The importance of V_1 is stressed, since the abnormalities in this lead may be the major ones. Precordial leads V_2, V_4 and V_5 may not be conclusive.

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Immunization of Human Beings with Group A Hemolytic Streptococci*

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WASHED broth cultures of strains of group A hemolytic streptococci of types 3 and 17 that had been

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demonstrated to produce large amounts of acid extractable, type specific protein, were heat killed and preserved with formalin. These were then injected subcutaneously in varying amounts into human beings at approximately weekly intervals for nine weeks. Serum was collected from each patient before the experiment and again four and ten weeks later. The presence of type specific antibodies was determined by the Rothbard technic. Precipitin tests using a non-type specific non-carbohydrate antigen present in acid extracts of group A hemolytic streptococci were also carried out.

Two subjects received vaccine of type 3, and two of type 17 equivalent to .37 mg. or more of bacterial N. Type specific antibodies appeared in all. The administration of the type 17 vaccine in amounts from .09 to .19 mg. N to three persons failed to stimulate the formation of measurable antibody. A similar range of dosage of type 3 vaccine was administered to four persons, one of whom developed type specific antibodies.

The results following immunization with the two types were similar with respect to the stimulation of precipitin formation. Four of seven of the study group who received the largest amounts of vaccine developed antibodies that reacted with substances contained in purified acid extracts of streptococcal cells. This antibody was present in four other individuals before immunization was begun. That it was not anti-"M" antibody is demonstrated by the fact that precipitation occurred with materials obtained from several different serological types.

Highly purified group carbohydrates prepared by Fuller's method and tested in suitable dilutions failed to induce precipitation with any serum obtained from ten subjects. In the eleventh, a reaction was obtained with both early and late sera.

In another similar study, thirty-two subjects received type 17 vaccine equivalent to .006 to .204 mg. N in three to five injections at weekly intervals. No antibodies of any kind developed in these persons.

The vaccines produced severe local reactions characterized by erythema and subcutaneous nodule formation in many persons. Striking differences existed in the amount of vaccine accepted by various subjects. Certain individuals who were able initially to accept large doses of vaccine without difficulty later reacted violently to similar or much smaller quantities of the antigen. This is believed to represent artificially induced hypersensitivity to group A hemolytic streptococci in man.

Effects of Acute Anoxia on the Capillary Permeability of the Human Arm*

J. P. HENRY, M.B., J. GOODMAN, PH.D. *and* J. P. MEEHAN

THE cuff technic of Landis et al. (*J. Clin. Investigation*, 11: 717, 1932) was employed to study the effects of anoxia on capillary permeability. Preliminary experiments were made to determine whether consecutive applications of congestion would give consistent results. Four subjects were submitted at sea level to thirty minutes of venous congestion (60 mm. Hg) twice repeated, with a rest period of sixty minutes between experiments. Duplicate hematocrit, hemoglobin and plasma protein estimations were made on blood samples from both control and congested arms. The mean fluid loss found in six such double experiments was in the first experiment 5.8 $\pm$ 0.5 cc. and in the second 6.3 $\pm$ 0.6 cc.

In a second series, one of the two consecutive experiments was run at a simulated altitude such that the oximeter reading was 65 to 75 per cent hemoglobin saturation. The mean estimated fluid loss for ten experiments at altitude was 5.0 $\pm$ 0.8 cc. The corresponding sea level value for this experimental series was 5.4 $\pm$ 0.8 cc. Analysis of the standard error of the fluid loss results shows that there is less than 1 chance in 100 that the loss at sea level differs by more than 20 per cent from that at altitude, with degrees of arterial hemoglobin saturation of the order of 70 per cent.

In addition, a number of double experiments were carried out using an injection of adrenalin in peanut oil in one of the tests as a means of raising the blood pressure for the thirty-minute

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period of congestion. The fluid loss decreased very greatly when there was a marked rise, i.e., 20 to 30 mm. Hg in the blood pressure. This might explain the sharp decrease in fluid loss sometimes observed with severe anoxia, since in acute anoxia the blood pressure may increase by this amount.

Effect of Local Cooling on Fluid Movement in the Human Forearm*

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THE pressure plethysmograph was used to study the effect of cold on capillary permeability in man. The volume of a segment of forearm could be measured during application of a pressure of 200 mm. Hg to the water within the plethysmograph so that changes in extravascular fluid content, exclusive of vascular volume, were determined. Readings were made during application of pressure for two-minute periods which were separated by intervals of eight minutes. At plethysmograph temperatures of 34°, 24°, 14° and 4°C., "reduced arm volume" was measured in four normal subjects at ten-minute intervals (1) under resting conditions and (2) before and after raising venous pressure 20, 40 or 60 cm. water above resting level.

In order that venous pressure and initial tissue pressure might be as uniform as possible, the mid-point of the forearm segment was level with the manubrium sterni and the subject was prepared by a ninety-minute period of recumbency during which the arm was supported in this position. Even when these precautions were taken, there was a slight progressive decrease in reduced arm volume averaging .008 cc. per 100 cc. of arm per minute during eighty-minute observation periods at 34°C. This was related to the number of readings and not to elapsed time and was thought to be due to squeezing out of soft tissues by the pressure.

At temperatures below 34°C., reduced arm volume decreased less rapidly or actually increased. In every subject, a relative increase was apparent at 24°C. and swelling was successively greater at 14° and 4°C. The average net increase in volume after sixty minutes at 4°C. was 1.03 cc. per 100 cc.

To determine the rate of filtration of fluid per unit rise of venous pressure, reduced arm volume was measured before and immediately after ten-minute periods of venous congestion. At 34°C. the average increase in volume per cm. rise in venous pressure was .0027 cc. per 100 cc. per minute. At 4°C. the unit filtration rate was reduced more than 30 per cent. After release of congestion, the rate of reabsorption per cc. of accumulated excess tissue fluid was less at 24°C. or below than at 34°C. In some instances at 4°C., there was no recovery and the arm continued to swell.

The increase in extravascular volume at constant venous pressure and impairment in reabsorption of excess tissue fluid found during cooling are most readily attributed to cellular injury with increased permeability of the capillary walls to protein and consequent reduction in effective osmotic pressure of the blood. Absolute proof of the presence of protein in the capillary filtrate is lacking and other factors must be considered. Even in the least sensitive subjects, abnormalities of fluid movement appeared at plethysmograph temperatures as high as 24°C. The decrease in unit rate of filtration observed during local cooling may be the result of (1) increased tissue pressure from edema fluid formed in the cold before congestion was begun, or (2) reduction in total area of capillary wall available for filtration.

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A Survey of Commercial Rh Antisera*

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A SURVEY of the blood grouping characteristics of all pregnant women on the obstetrical service of the White Memorial Hospital and clinic led to difficulty in obtaining sufficient Rh typing serum. When serum from various manufacturers was used, certain inconsistencies soon became apparent. A comparative study of all available commercial Rh typing sera was undertaken.

Six different antisera from four different manufacturers were tested on a total of 1,099

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bloods from patients. One antiserum was produced in guinea pigs; all others were antisera of human origin. All tests were run according to the instructions of the manufacturer. Tests were read macroscopically and microscopically before and after centrifuging at 1,000 r.p.m.

The guinea pig serum gave positive reactions in all infants up to one month of age. This is in accordance with findings first reported by Fisk and Foord. This same guinea pig serum gave 85.7 per cent positives in the adult series. The antisera of human origin gave 88.7, 88.0, 80.2, 27.3, 44.7 and 10.0 per cent positive reactions, respectively. The last two observations listed were of tests on the same antiserum, the former using concentrated and the latter diluted antiserum according to the instructions of the manufacturer. Those antisera giving nearest 85 per cent positives showed certain inconsistencies, each giving some negative reactions with bloods which were positive with others. Titrations by the standard test tube method gave results varying from 1:4 to 1:32. All antisera were used within the expiration date set by the manufacturer.

Variations reported here may be due wholly or in part to variations in initial strength of the serum, deterioration of serum and failure to recognize the Rh subgroups in labeling the antisera. Slight variations in technic invariably lead to inconsistencies in the results of Rh typing procedures.

This study emphasizes the need of some central control of the standardization, assay and labeling of Rh testing antisera. Such control together with a standard technic should largely eliminate the conflicting results now encountered in Rh testing with commercial antisera.

Effects of Dibenamine (Dibenzyl-beta-chloroethyl amine) on Human Subjects (Preliminary Report) *

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A SERIES of tertiary amines, structurally related to nitrogen mustards (bis- or tris-chloroethyl-amines) has recently been introduced with the claim that compounds of this structure would block or reverse certain excitatory adrenergic responses in animals ("sympatholytic" action). One of these agents, dibenzyl-beta-chloroethyl amine ("Dibenamine") was made available to us for clinical trial and has been administered to fifty-four patients.

Intravenous administration was found to be the only route which was safe and which gave consistent and predictable results. The dose which can be tolerated appears to be 4 to 6 mg/kg., which is only one-fifth of the dose usually employed in animal experiments. A detailed study of the effect of this agent on the activity of the sympathetic nervous system was made in thirty-five patients who received a total of sixty-two injections.

In these patients and in the doses given, dibenamine appeared to block certain manifestations which occur upon the administration of epinephrine or other sympathomimetic compounds. Among those for which complete protection was afforded were (1) pupillary dilatation in dim light; (2) rise in arterial pressure induced by sympathomimetic compounds; (3) rise in venous pressure; (4) reflex (vagal) bradycardia with the development of independent ventricular rhythms and (5) reflex (vagal) changes of the T waves. In almost all instances postural reflexes were inhibited and pronounced orthostatic hypotension with positive Flack test developed. The blocking effect lasted for about twenty-four hours, rarely longer. An incomplete inhibition of sweat secretion was observed and the incidence and number of ectopic cardiac foci, readily induced by injection of epinephrine, could be reduced but not abolished. Dibenamine in the doses given failed to influence (1) rise in blood sugar; (2) rise in cardiac output; (3) capillary constriction; (4) tachycardia; and (5) depression of the S-T segment and lengthening of the Q-T interval. The resting arteriolar tone was not altered appreciably.

In doses that can be administered safely dibenamine appears to be an agent which prevents vasoconstriction and which may at times cause temporary vasodilatation. Certain other effects make it appear likely that compounds of this kind possess limited sympatholytic properties.

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Observations on Patients during Streptomycin Therapy*

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TWENTY-SEVEN patients were treated with streptomycin. Each suffered from infection caused by an organism which was sensitive to streptomycin by *in vitro* test. These infections were as follows: (1) Systemic infections: These were brucellosis with bacteremia, typhoid fever, H. influenzae type b meningitis, E. coli and Aerobacter aerogenes sepsis and A. aerogenes endocarditis. (2) Urinary tract infections shown to be resistant to sulfonamides or in patients sensitive to these drugs. (3) Miscellaneous infections: These included one patient suffering from postoperative conjunctivitis and iritis caused by Pseudomonas aeruginosa in whom streptomycin was employed locally only and one patient with empyema and lung abscess in whom the predominant organism was E. coli.

The patients were studied throughout the course of infection, repeated cultures were made and the organisms tested for sensitivity to streptomycin. The level of streptomycin in the blood was measured occasionally. An attempt was made to correlate the *in vitro* sensitivity of organisms and the development of resistance under treatment with cultural and clinical outcome. The effects of streptomycin, both toxic and therapeutic, were observed.

The observations suggested certain therapeutic results. One patient with bacteremic brucellosis appeared to respond and has maintained an uneventful convalescence without relapse for four months. He received 5 Gm. of streptomycin in 1,000 cc. of physiological saline solution per day by continuous intramuscular infusion for fourteen days. The response may have been due to his tolerance for a moderately large dose of streptomycin administered continuously for two weeks. Another patient with bacteremic brucellosis failed to improve and blood cultures remained positive. He developed a sharp febrile reaction with maculopapular eruption when administered 3 Gm. daily by the continuous method. The course of typhoid fever in two patients did not seem to be affected by therapy. Streptomycin appeared specifically effective in four cases of H. influenza type b meningitis. One patient with subacute bacterial endocarditis due to A. aerogenes improved rapidly with streptomycin and remained well during a short period of observation.

Acute or chronic urinary tract infections due to E. coli or A. aerogenes responded quickly and showed little tendency to relapse when the urinary tract was structurally normal. In such circumstances the urine became sterile within a few hours, even when several million organisms per cc. of urine were present before treatment. When structural abnormalities were present, however, recurrence of infection occurred. At this time the resistance of the organisms to streptomycin was found to be increased many fold. Pseudomonas aeruginosa became resistant very quickly and recurrence developed more frequently when it was the infecting organism.

Streptomycin was given by continuous intramuscular infusion, intermittent intramuscular injection, intraspinally and intrapleurally. Only two significant reactions were encountered. Fever and eruption occurred in one patient and mild temporary ataxia in another. Both patients suffered from brucellosis and both received streptomycin by continuous intramuscular injection.

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Mechanism of the Development of Resistance to Streptomycin*

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THE development of resistance to streptomycin is of practical as well as theoretical importance, since it has been observed that resistant strains of pathogenic organisms develop with relative frequency after treatment with streptomycin. The exact mechanism of the development of resistance has not been determined, but it has been postulated that resistant strains of an organism might be found after exposure to some antibacterial agent

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because the organisms were: (1) naturally resistant; (2) rendered resistant by contact with an antibacterial substance; (3) obtained by natural selection; or (4) in an insusceptible phase at the time of exposure.

In studying the mechanism of the development of resistance of micro-organisms to streptomycin the method of testing was based on the twenty-four hour inhibition of growth of the organism when fertile hens' eggs were used as the culture medium. Using this method bacterial suspensions of colony mixtures of a single strain of Escherichia coli were found to be inhibited by 5 micrograms of streptomycin per chick embryo. The mixed suspension then was cultured on agar plates and 100 individual colonies were tested for their sensitivity to streptomycin. It was found that there was a marked variation of the sensitivities of the individual colonies. Although 62 per cent of the colonies were sensitive to between 2 and 8 micrograms of streptomycin per fertile egg, it was found that the most resistant colonies required over 100 times as much streptomycin as the most sensitive ones even though they were all isolated from the same strain. When the results of the sensitivity tests were plotted, they formed a standard curve of distribution. Similar distribution was noted when the individual components making up a resistant strain of E. coli were tested for their sensitivity to streptomycin. None of the organisms tested in these experiments had had any previous exposure to streptomycin and any resistance that was demonstrated was a natural characteristic of that particular component and had not been influenced by contact with the antibiotic.

These results support the theory that even sensitive strains of an organism originally contain resistant components. It was found that the sensitivities of the individual components of any organism formed a curve of distribution if these sensitivities are plotted. It is suggested that suspensions of colony mixtures rather than individual colonies should be used for tests of sensitivity to streptomycin in order to avoid the inadvertent testing of either extreme in the range of sensitivities of the various individual components, so that the average sensitiveness of the strain tested can be determined.

Plasma Angiotonase Concentration in Normal and Toxemic Pregnancies*

ERNEST W. PAGE, M.D.

ANGIOTONASE is the term applied to that component of the renal pressor system capable of inactivating angiotonin. Despite the widespread distribution and high activity of angiotonase in various tissues, we have shown that only the small amount of enzyme which is free in the plasma is normally available for angiotonin destruction. If the "deficiency theory" of human hypertension accounted for the elevation of blood pressure in eclampsia, reduced plasma concentrations of angiotonase should be encountered in that disease.

A method based upon the kinetics of angiotonase activity has been applied to the measurement of plasma concentration in ten healthy non-pregnant subjects, sixteen normal pregnancies and ten cases of pre-eclampsia or eclampsia. In normal pregnancy, there is a four to eightfold increase in angiotonase activity. In eclampsia, there is a wider range of concentrations, but no correlation between the enzyme level and the degree of hypertension.

If plasma angiotonase is the primary means by which circulating angiotonin is destroyed, it would be anticipated that pregnant women would respond to intravenously injected angiotonin with a blood pressure rise of relatively short duration. This was tested and found to be true.

It is concluded that a deficiency of angiotonase is not the cause of the hypertension in eclampsia.

Relation of the Distribution of Crash Injuries in Man to Those Observed in Animals during Experimental Deceleration†

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IN the past, information concerning the nature and characteristics of desirable protective devices and the methods of

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treating internal injuries of various types has been obtained largely by studies of accidents and their victims. During the recent war, a series of experiments was conducted on experimental animals (anesthetized cats) exposed to sudden deceleration under controlled conditions to determine if the nature of the injuries produced bore any relation to those observed in humans coming to autopsy following aircraft accidents.

It was noted that lesions in the lungs predominated in both humans and animals and were characterized by profuse interstitial hemorrhages, the distribution of which did not appear to bear any particular relation to the direction of action of the force. In humans, traumatic emphysematous areas were quite frequently found and were occasionally seen in the animals. Lacerations and herniation of the diaphragm were encountered in both series. Lacerations of the capsule of the liver and spleen and extending into the parenchyma were characteristic findings in both man and cat.

Traumatic lesions in the brain, heart, gastrointestinal tract and skeleton were frequently encountered in humans but could rarely be produced in the animals under the conditions obtaining in the experiments. In no case was the severity of these injuries comparable to those produced in humans. This was attributed to the fact that the velocity at impact, the duration of the force and the mass and degree of relaxation of the body of the animals were markedly different than those encountered in aircraft accidents.

The evidence presented indicated that, given sufficient velocity at impact, the lesions which are so frequently observed in any type of exposure to force may be reproduced in animals with sufficient accuracy to allow investigation of means of protection and method of treatment.

Serologic Reactions in Trichinosis*

ARTHUR W. FRISCH, M.D.

An epidemic of mild trichinosis among a large group of prisoners of war offered an unusual opportunity to study the serologic response to the disease under relatively controlled conditions. A total of 250 cases were followed during the acute phase, three, six, and twelve weeks later by means of intradermal, precipitin and complement fixation tests. Positive immediate skin responses were obtained in 42 to 50 per cent of patients using an alkaline saline extract of trichina larvae which had been placed in boiling water to remove heat precipitable material. Antigens prepared by the methods commonly employed differed markedly in activity from each other and lacked sensitivity. The maximal incidence of positive complement fixation reactions was 37 per cent whereas the highest value of the precipitin test never exceeded 6 per cent. As a result of the experience gained, a re-evaluation of serologic procedures for the diagnosis of trichinosis appears to be necessary.

Additional studies with purified extracts in the form of an acid soluble protein and a polysaccharide revealed that they did not constitute the active component. The fraction of trichina larvae responsible for complement fixation proved to be heat stable and precipitable with acetone and alcohol. On the basis of these findings a practical approach to the problem of obtaining standardized trichina extracts is presented.

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Collateral Circulation of the Normal Human Heart*

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The collateral circulation in the normal human heart has been examined by the use of technics previously not reported: (1) perfusion of the coronary vessels with human radioactive red cells to determine the presence of anastomotic channels, and (2) an injection mass containing glass spheres of varying diameter to determine the size of such anastomotic channels.

Human erythrocytes made radioactive by incubation with radiophosphorus (P^{32}) were perfused through either the anterior descending

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or circumflex branch of the left coronary artery and the distribution of erythrocytes was determined by means of (1) Geiger counts at arbitrarily chosen areas on the pericardial and endocardial surfaces, and (2) radio-autographs of the unrolled heart. Abundant amounts of the labelled erythrocytes were found throughout the left ventricle, indicating numerous anastomoses within the left ventricle; and some radioactivity was present in the vascular tree of the right ventricle, confirming the existence of anastomotic channels between the right and left ventricles.

Glass spheres 10 to 440 micra in diameter were suspended in a radiopaque gelatin mixture, perfused through one of the coronary arteries of normal human hearts (four to seventy-three years of age) at physiologic pressures, and collected from the opposite coronary artery, the coronary sinus and the ventricular cavities. Spheres of 70 to 180 micra in diameter were recovered from the opposite coronary artery, 70 to 170 micra from the coronary sinus and 70 to 220 from the ventricular cavities. These findings indicate the existence of intercoronary anastomoses of arteriolar dimensions in the normal human heart. Also the presence of arteriovenous anastomoses is demonstrated. In preliminary studies in coronary arteriosclerosis and ventricular hypertrophy, glass spheres of 120 to 150 micra were recovered from the opposite coronary vessel.

Alterations in the Arterial Pulse Wave in Patients with Cardiovascular Disease*

GEORGE S. EDWARDS, M.D.
(*Introduced by R. Drury*)

IT was noted during an investigation of blood pressure determinations with a recording oscillometer that there were considerable variations in the configuration of the arterial pulse wave. Investigation of these changes were undertaken. Initially a purely mechanical recording device (sphygmoscope) was utilized. Even with such a relatively insensitive instrument, characteristic wave patterns were found in certain specific pathological conditions. Sufficient data were obtained to make continuation of the problem seem desirable. To this end a far more sensitive instrument was developed which incorporated a differential chamber and optical recording system.

Cases studied included examples of coarctation of the aorta, patent ductus arteriosus, traumatic occlusion of the terminal aorta, congenital enlargement of the brachial artery, calcific aortic stenosis, aneurysms of the aortic arch, aortic regurgitation, postural hypotension, malignant hypertension, occlusive vascular disease in diabetics and non-diabetics, and a large number of instances of hypertensive and arteriosclerotic cardiovascular disease and instances of rheumatic heart disease with mitral and/or aortic lesions. In those cases in which autopsies were obtained, the predicted pathological condition was demonstrated.

It is believed that alterations in arterial wave form are an important diagnostic adjunct and have definite prognostic value in certain types of early cardiovascular disease.

In order to evaluate more critically the factors concerned in those pulse wave changes, refinements in instrumentation are being carried out. Further studies are under way which incorporate simultaneous recordings of direct and indirect arterial pulse waves at two or more points, together with venous pressure measurements and digital plethysmographs.

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Direct Measurement of Blood Pressure within Arterial Aneurysms and Arteriovenous Fistulas*

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A METHOD is described for the direct measurement of pressures within arterial aneurysms and arteriovenous fistulas. A three-way stopcock is fitted with short lengths of rubber tubing connecting a No. 20 gauge needle with a 10 cc. syringe. To the third arm is attached an anaeroid manometer similar to that used with a blood pressure cuff. The manometer is not sterile, but it is enclosed in a sterile transparent oiled silk cover.

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The blood pressure within aneurysmal sacs was measured at the time of operation in twelve patients with arterial aneurysms and eleven patients with arteriovenous fistulas. The mean initial pressure in the group with the arterial aneurysms averaged 84 mm. of Hg, with variations between 110 and 34 mm. of Hg. Upon constriction of the afferent artery the pressure fell to an average of 58 mm. of Hg. In the patients with arteriovenous fistulas the mean initial pressure averaged 40 mm. of Hg with variations between 70 and 30 mm. of Hg. With constriction of the afferent artery the pressure fell to an average of 10 mm. of Hg.

Determination of the intra-aneurysmal pressure following temporary occlusion of the component vessels has been found useful not only in estimating the degree of development of collateral circulation but also in disclosing the presence of unsuspected collateral vessels which empty into the aneurysmal sac and which have to be controlled before the aneurysm can be safely opened.

The lowest mean arterial pressure found after excision of an aneurysm or arteriovenous fistula was 32 mm. of Hg. With pressures at or above this level, adequate circulation of blood to the peripheral tissues while at rest has been observed in these patients. However, although no case of gangrene was observed with such low pressures, there was evidence of impaired circulation in two patients, as shown by absent pulses and increased fatigue following muscular activity.

Diagnosis of Pancreatic Disease by Enzyme Tests*

LESTER M. MORRISON, M.D.

OVER 1,000 pancreatic enzyme tests were made on the duodenal secretions in a group of normal subjects, a group of patients with "functional" or non-organic disease of the upper digestive tract and a group of patients with organic disease of the pancreas, biliary tract, stomach or duodenum.

The range and mean of duodenal pancreatic enzyme tests for normal subjects and patients suffering from upper digestive tract disorders is described. A recent method of estimating pancreatic enzymes, introduced by Free, Beams and Myers is employed and substantiated in this series of cases.

The findings in a group of ten patients with chronic, low-grade or moderate inflammation of the pancreas as revealed at operation are recorded. The duodenal enzyme studies in these cases failed to show any consistently abnormal findings of diagnostic value, either before or after operation.

Normal subjects as well as patients with extensive and severe pathological involvement of the pancreas like cancer may give zero or near zero test readings in individual duodenal pancreatic enzyme tests.

In patients with organic disease of the stomach or biliary tract, pancreatic duodenal enzyme tests revealed no individual distinctive or diagnostic findings. However, their group mean value was definitely lower than the comparable value in normal subjects.

In six cases of extensive involvement of the pancreas by cancer, or cirrhosis with pancreatic lithiasis, 125 tests gave abnormal findings in the duodenal pancreatic enzyme tests. These abnormal findings were either zero or near zero values.

If a zero reading was found in the pancreatic enzyme tests of a normal subject, it was not consistently found in all subsequent determinations.

In the presence of advanced and extensive pancreatic disease such as cancer or cirrhosis, zero or near zero readings were found consistently in all subsequent determinations.

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Treatment of Rheumatoid Arthritis with Massive Doses of Salicylates —with Particular Reference to Modification of Plasma Protein Constituents during Therapy*

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ABNORMALITIES of the blood frequently are observed in patients with rheumatoid arthritis. Often there is moderate anemia and an elevated erythrocyte sedimenta-

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tion rate. The plasma fibrinogen tends to be elevated. Frequently there is a moderate reduction in serum albumin and an increase in total serum globulin. The gamma globulin fraction, in particular, may be greatly elevated.

During the past eighteen months we have treated sixteen cases of rheumatoid arthritis with massive doses of salicylates. The clinical response occasionally was excellent; however, improvement usually was less striking and was partially offset by the unpleasant symptoms of salicylate intoxication. Anemia was found to disappear in those patients in whom this was present at the beginning of therapy. Changes in plasma fibrinogen and erythrocyte sedimentation rate during therapy were variable. Usually it was possible to demonstrate that during the course of salicylate therapy the initially low serum albumin returned to a normal value while the initially elevated serum globulin decreased toward normal values. Likewise the "gamma globulin" fraction of serum as determined chemically usually was greatly elevated prior to therapy and decreased during treatment with salicylates.

It was not possible to maintain desired plasma salicylate levels in every patient during therapy. It appeared, however, that return of these blood constituents to normal values occurred more frequently in those patients in whom high plasma salicylate levels could be maintained. With cessation of therapy, clinical relapses occurred frequently and the blood constituents tended to return to their pre-treatment values.

We do not imply that massive doses of salicylates constitute a superior form of therapy in the treatment of rheumatoid arthritis. Nevertheless the changes produced by salicylates deserve further study as regards the mechanism of production of arthritis as well as the mechanism of action of sodium salicylate.

Hyperplasia of the Gastric Mucosa in Man*

ALVIN J. COX, M.D.

A QUANTITATIVE study of 130 human stomachs obtained at autopsy soon after death has shown a broad range in the quantity of mucosal tissue. The quantitative difference is most pronounced in the specific secretory portion of the mucosa. An expression of the amount of acid secreting tissue in each stomach was obtained by estimating the total number of parietal cells. Fourteen cases of active or healed duodenal ulcer all had parietal cell numbers in the upper portion of the range, while nine cases of chronic gastric ulcer had no uniform distribution.

No constant relationship could be recognized between the amount of mucosal tissue and the degree of cellular infiltration, so it is concluded that hyperplasia and gastritis are manifestations of separate processes, and the term "hypertrophic gastritis" is misleading.

* From the Department of Pathology, Stanford University School of Medicine, San Francisco, Calif.

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The American Journal of Medicine

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Volume II

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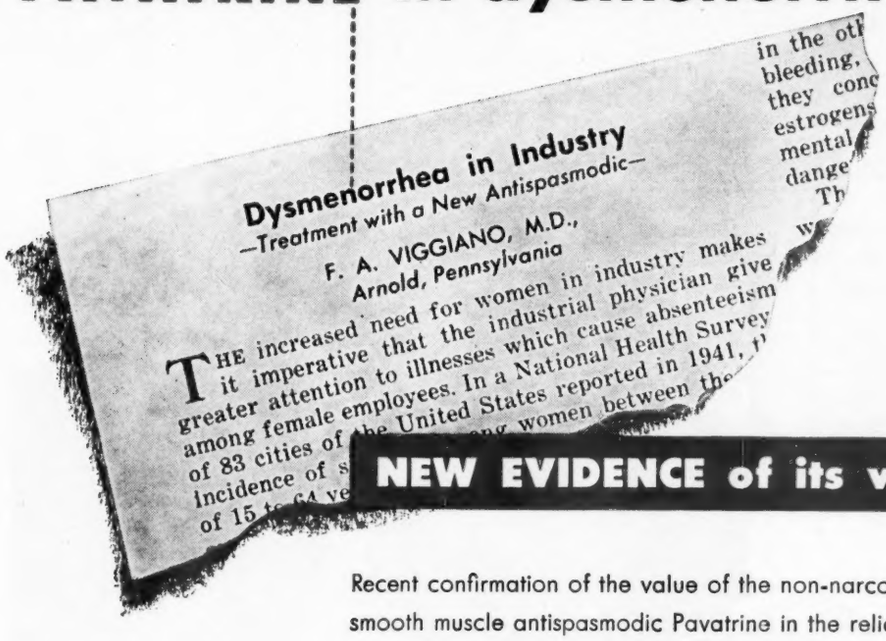
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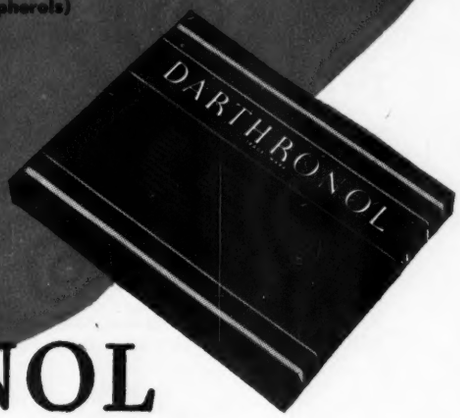

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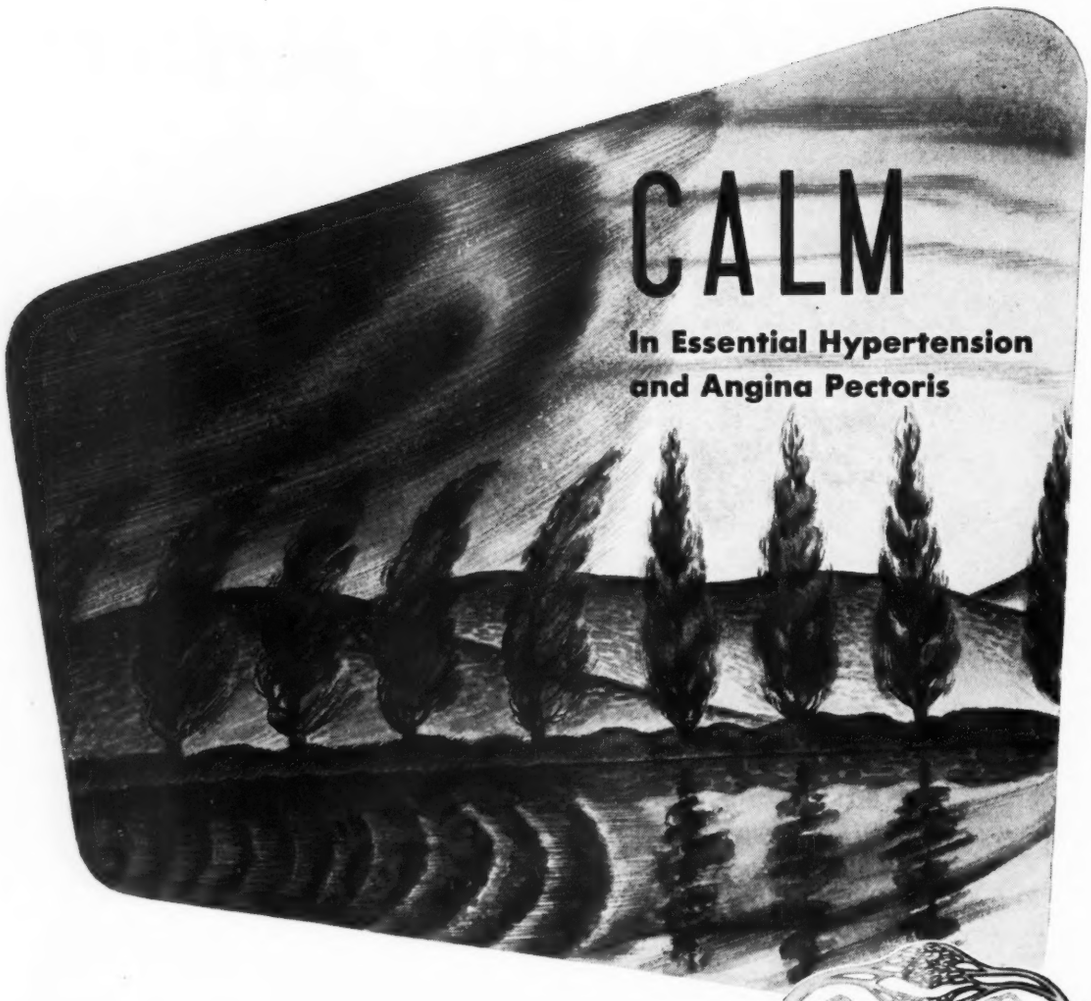

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IN

THE AMERICAN JOURNAL OF SURGERY

A SYMPOSIUM ON

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Edited by Francis M. Rackemann, M.D.
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and

Robert A. Cooke, M.D., Roosevelt Hospital
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They showed that sales of Savings Bonds went from $494 million in last September to $519 million in October and kept climbing steadily until, in January of this year, they reached a new postwar high: **In January, 1947, Americans put nearly a billion dollars in Savings Bonds. And that trend is continuing.**

In the same way, redemptions have been going just as steadily downward. Here, too, the trend continues.

Moreover, there has been, since the first of the year, an increase not only in the volume of Bonds bought through Payroll Savings, but in the number of buyers.

How about you?

The figures show that millions of Americans have realized this fact: there is no safer, surer way on earth to get the things you want than by buying U. S. Savings Bonds regularly.

They are the safest investment in the world. Buy them regularly through the Payroll Plan, or ask your banker about the Bond-a-Month Plan.

Save the easy, automatic way—with U.S. Savings Bonds

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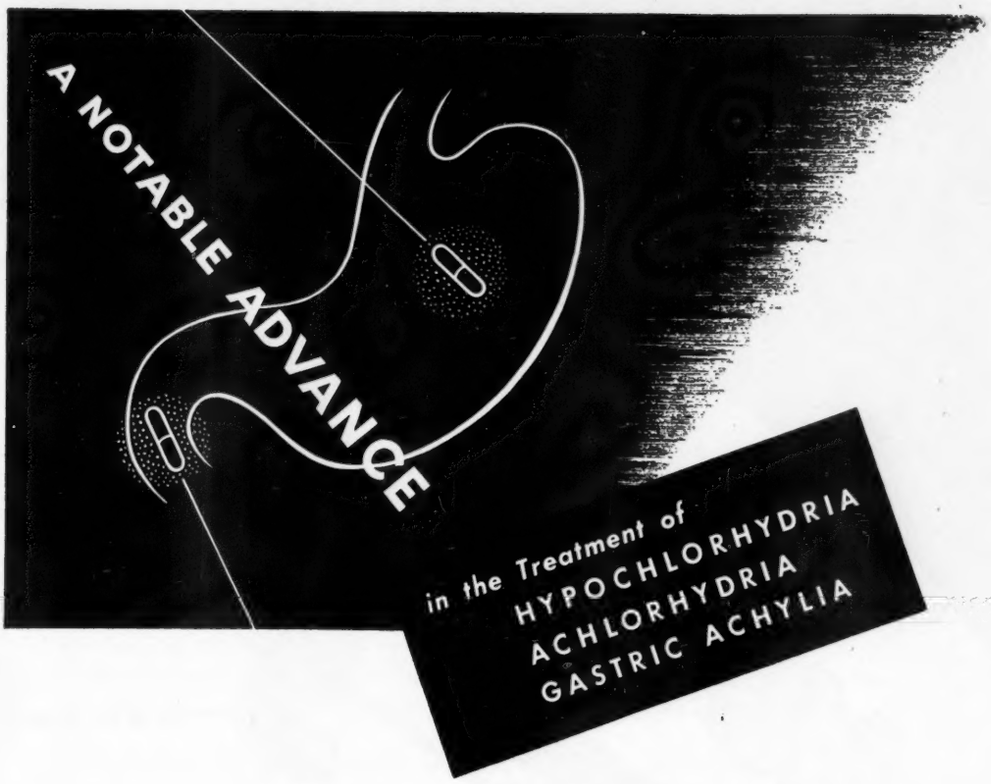

Maximal convenience in administration and increased clinical effectiveness are afforded in conditions marked by deficient gastric secretion by—

GLUTASIN*

Capsules Glutasin provide available hydrochloric acid in powder form as glutamic acid hydrochloride, which, upon contact with water or stomach juices, yields free HCl. Recent work indicates greater effectiveness when the acid is given together with pepsin.[1, 2]

It is especially noteworthy that hypovitaminosis of the B complex vitamins is increased in patients with achlorhydria since normal acidity is needed for maximal absorption and assimilation.

Indications: **Dyspepsia, flatulence, nausea of pregnancy, hypocalcia, achlorhydria and anemias. Contraindicated in obstruction of esophagus and in gastric and duodenal ulcers.**

Capsules Glutasin are available in bottles of 100, 500 and 1000.

1. Edmunds, C. W. and Gunn, J. A. CUSHNY'S PHARMACOLOGY AND THERAPEUTICS Philadelphia, Lea and Febiger, 11th ed., p. 255

2. Clark, A. J. APPLIED PHARMACOLOGY Philadelphia, P. Blakiston's Son & Co., Inc., 6th ed., p. 295

Each capsule contains Glutamic Acid Hydrochloride, 5 gr. and Pepsin U. S. P. 1 gr.

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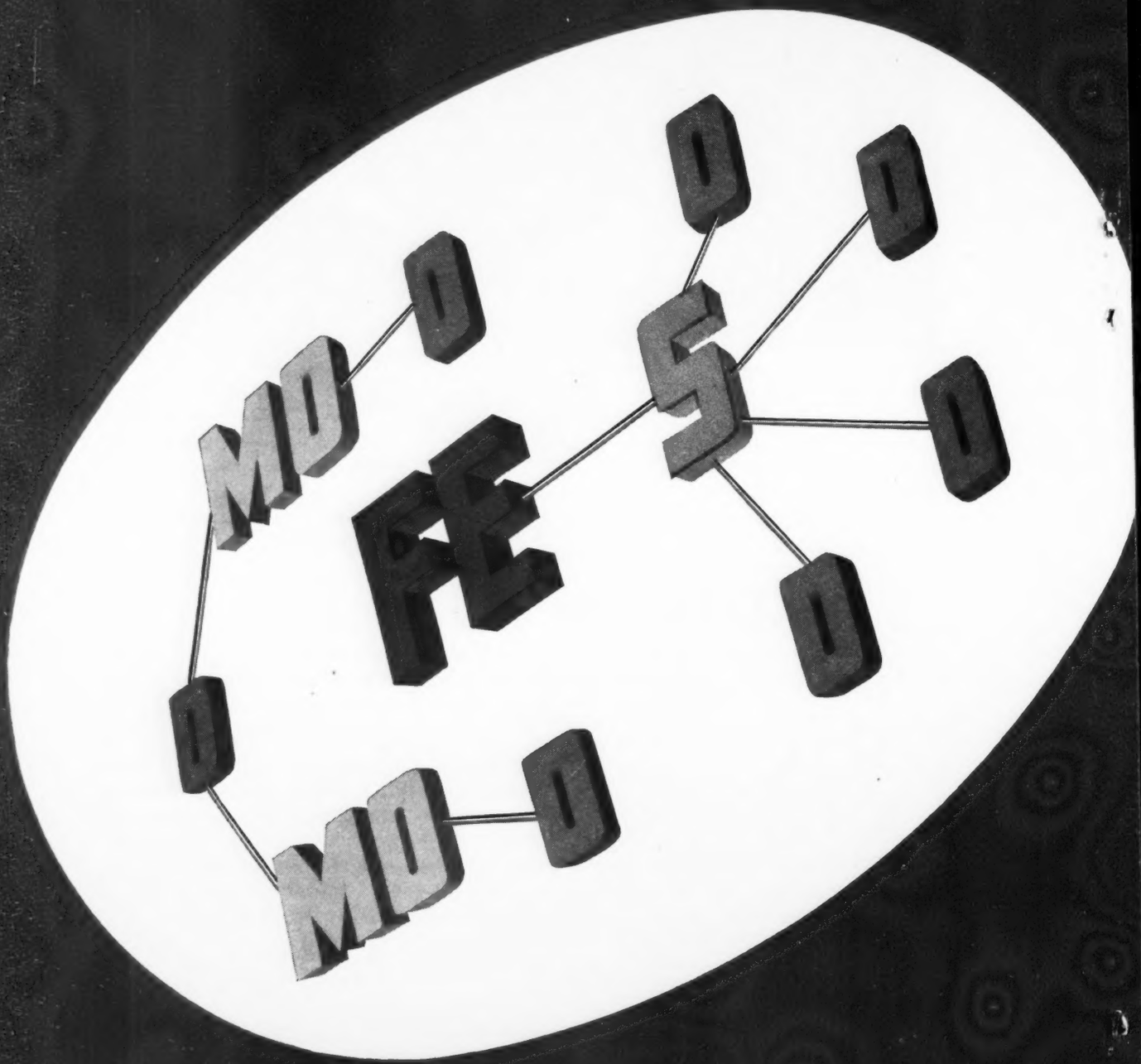
PHILADELPHIA 32, PENNSYLVANIA

demonstrably superior



White

White's

LABORATORIES, INC., Pharmaceutical Manufacturers, Newark 7, N. J.

iron utilization in hypochromic anemias

Controlled clinical studies conducted on patients with hypochromic anemia reveal the therapeutic superiority of molybdenized ferrous sulfate over equivalent dosages of ferrous sulfate alone:

MORE RAPID RECOVERY—Normal hemoglobin values are restored more rapidly, increases in the rate of hemoglobin formation being as great as 100% or more in patients studied.

INCREASED UTILIZATION—Iron utilization is similarly more complete.

BETTER TOLERANCE—Gastrointestinal tolerance is excellent—even among patients who have previously shown marked gastrointestinal reactions following oral administration of other iron preparations.*

White's Mol-Iron is a specially processed, co-precipitated complex of molybdenum oxide 3 mg. (1/20 gr.) and ferrous sulfate 195 mg. (3 gr.). Bottles of 100 and 1000 tablets.

Healy, J. C.: Hypochromic Anemia: Treatment with Molybdenum-Iron Complex, The Journal-Lancet, *66*:218-221 (July) 1946.

Mol-iron *Tablets*

(Molybdenized Ferrous Sulfate)

HIGHLY NUTRITIOUS . . .
YET PALATABLE AND SATISFYING

Dietary supplements, in order to accomplish their desired nutritional influence, must be tasty and appealing to the palate. Otherwise, refusal by the patient will defeat their very purpose and will limit nutrient intake.

The food drink made by mixing Ovaltine with milk ranks high in nutrient content and palatability. This dietary supplement provides generous amounts of virtually all essential nutrients including ascorbic acid, in readily digestible, thoroughly bland form. Its delicious taste is appealing to all patients, young and old, who drink it with relish in the recommended quantities—two to three glassfuls daily. This amount, as can be seen from the table of composition, readily complements to adequacy even a poor daily dietary.

This nutritional supplement finds application when nutrient intake must be raised, in sub-nutrition, after recovery from infectious disease, and during chronic debilitating illness.

THE WANDER COMPANY, 360 N. MICHIGAN AVE., CHICAGO 1, ILL.

Ovaltine

Three servings daily of Ovaltine, each made of ½ oz. of Ovaltine and 8 oz. of whole milk,* provide:

CALORIES	669	VITAMIN A	3000 I.U.
PROTEIN	32.1 Gm.	VITAMIN B_1	1.16 mg.
FAT	31.5 Gm.	RIBOFLAVIN	2.00 mg.
CARBOHYDRATE	64.8 Gm.	NIACIN	6.8 mg.
CALCIUM	1.12 Gm.	VITAMIN C	30.0 mg.
PHOSPHORUS	0.94 Gm.	VITAMIN D	417 I.U.
IRON	12.0 mg.	COPPER	0.50 mg.

*Based on average reported values for milk.

For the Patient's *Sense of Well-Being*

Few are the clinical conditions in which the luxury of enjoying candy appears contraindicated.

During convalescence when appetite so often lags or become capricious, and the complaint is voiced that "nothing seems to taste good," candy as a rule is eaten with gusto, and appears doubly worth while. It presents high caloric value in small bulk and is easily digested—furthermore, it is gratifying to note the psychic lift given the patient by even a small piece of candy.

Within the dietary framework permitted, candy—while contributing to the essential carbohydrate needs—also provides a delightfully satisfying diversion for the diabetic patient who is faced by dietary limitations.

Thus, though the small amounts of nutrients supplied by one or two pieces of candy may not be significant in the dietary regimen, the sense of well-being engendered by candy merits recognition in the light of the over-all clinical picture.

COUNCIL ON CANDY OF THE NATIONAL CONFECTIONERS' ASSOCIATION

1 NORTH LA SALLE STREET • CHICAGO 2, ILLINOIS

multiplication

The amount of B factors available to B vitamin depleted tissues may be quickly multiplied several fold with Solu-B* intravenously or intramuscularly.

Each vial of Solu-B contains:

Thiamine Hydrochloride	10 mg.
Riboflavin	10 mg.
Pyridoxine Hydrochloride	5 mg.
Calcium Pantothenate	50 mg.
Nicotinamide	250 mg.

or multiplied many more times with Solu-B 5x which contains precisely 5 times the quantity of each B vitamin present in Solu-B:

Thiamine Hydrochloride	50 mg.
Riboflavin	50 mg.
Pyridoxine Hydrochloride	25 mg.
Calcium Pantothenate	250 mg.
Nicotinamide	1250 mg.

*Trademark Reg. U. S. Pat. Off.

Upjohn
KALAMAZOO 99, MICHIGAN

FINE PHARMACEUTICALS SINCE 1886

solu-B

Solu-B powder is packaged in vials of 10 cc., each vial accompanied by one 5 cc. ampoule of sterile water; in boxes of 5 vials with 5 ampoules of sterile water; and in boxes of 25 vials of Solu-B without water. Solu-B powder is stable indefinitely and almost instantly soluble in most diluents.

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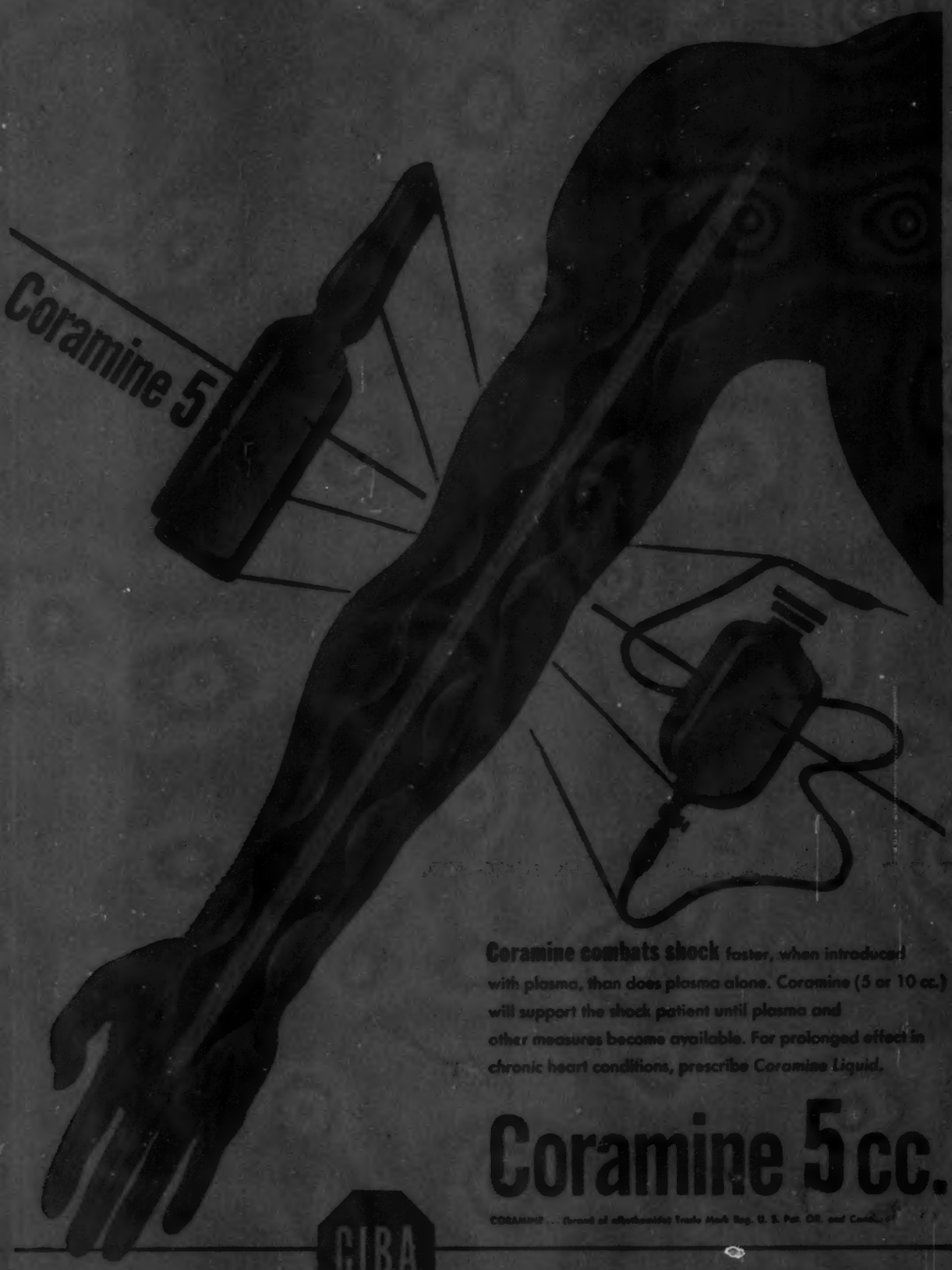

Coramine combats shock faster, when introduced with plasma, than does plasma alone. Coramine (5 or 10 cc.) will support the shock patient until plasma and other measures become available. For prolonged effect in chronic heart conditions, prescribe Coramine Liquid.

Coramine 5 cc.

CORAMINE ... Brand of nikethamide Trade Mark Reg. U. S. Pat. Off. and Canada

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For further information, write Professional Service Department.

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